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KOMPLEXNÍ KARDIOVASKULÁRNÍ CENTRUM
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Antitrombotická terapie u FS: Novinky 2017

Miloš Táborský

České kardiologické dny

20.11. 2017

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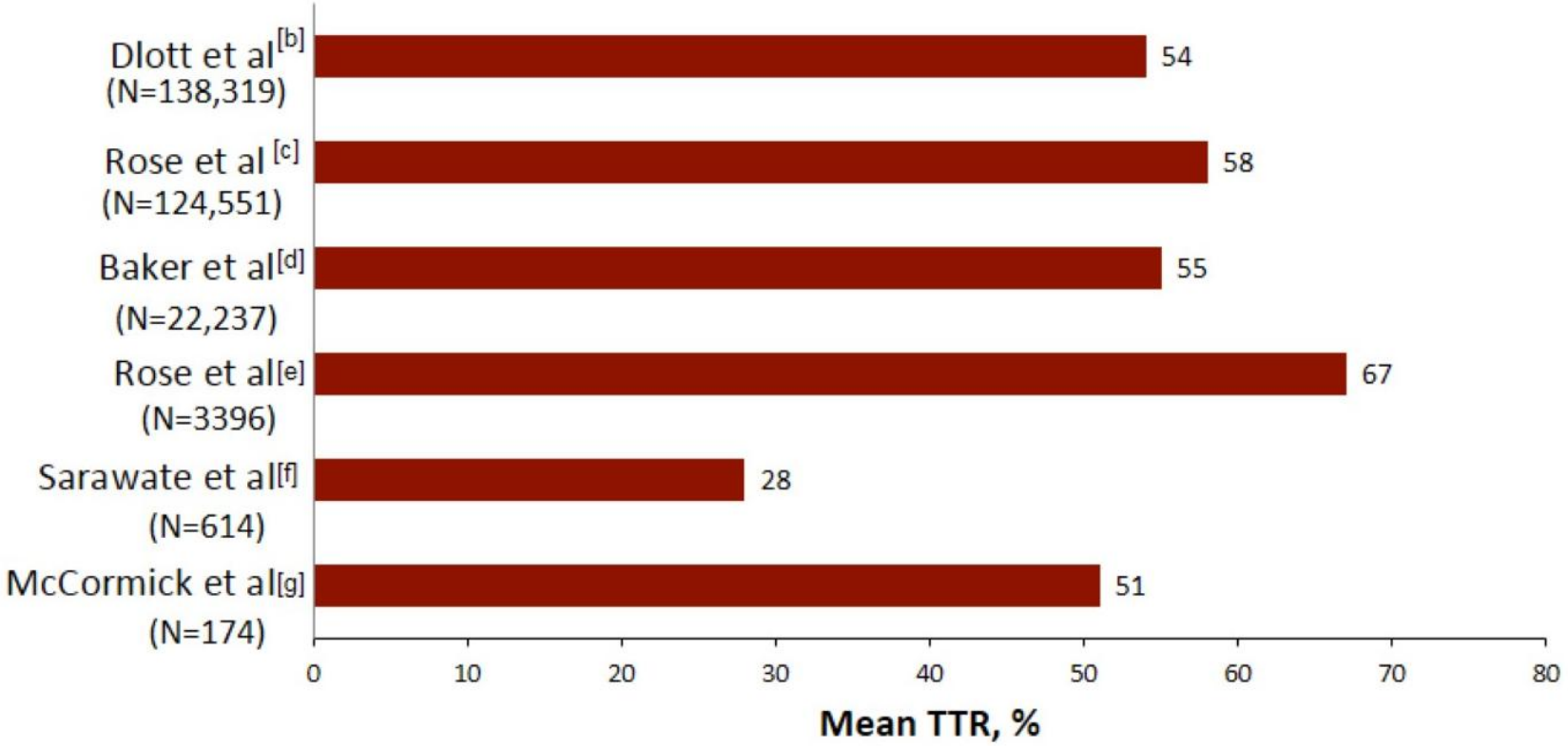
I: Data z reálné klinické praxe

Kontrola INR není zdaleka ideální

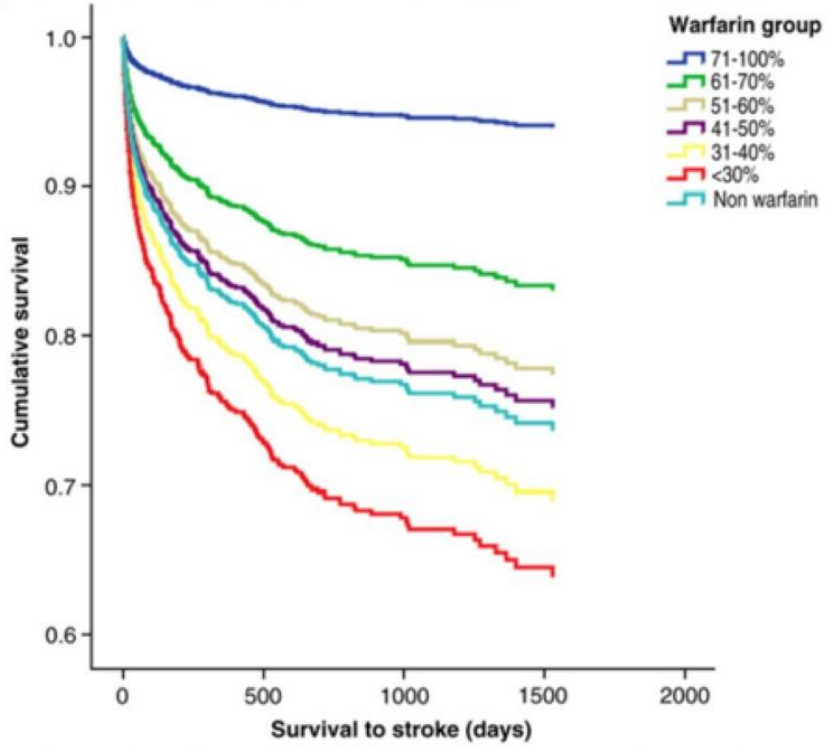
Meta-analysis shows that only 56% of measured INRs are within the ideal range[a]



Mearns ES, et al. Thromb J. 2014;12:14

Terapeutický efekt warfarinu je výrazně závislý na TTR

In patients with AF and $CHADS_2$ ≥2, only patients who maintained TTR >70% experienced significant improvement in time to stroke compared with the no-warfarin treatment group*

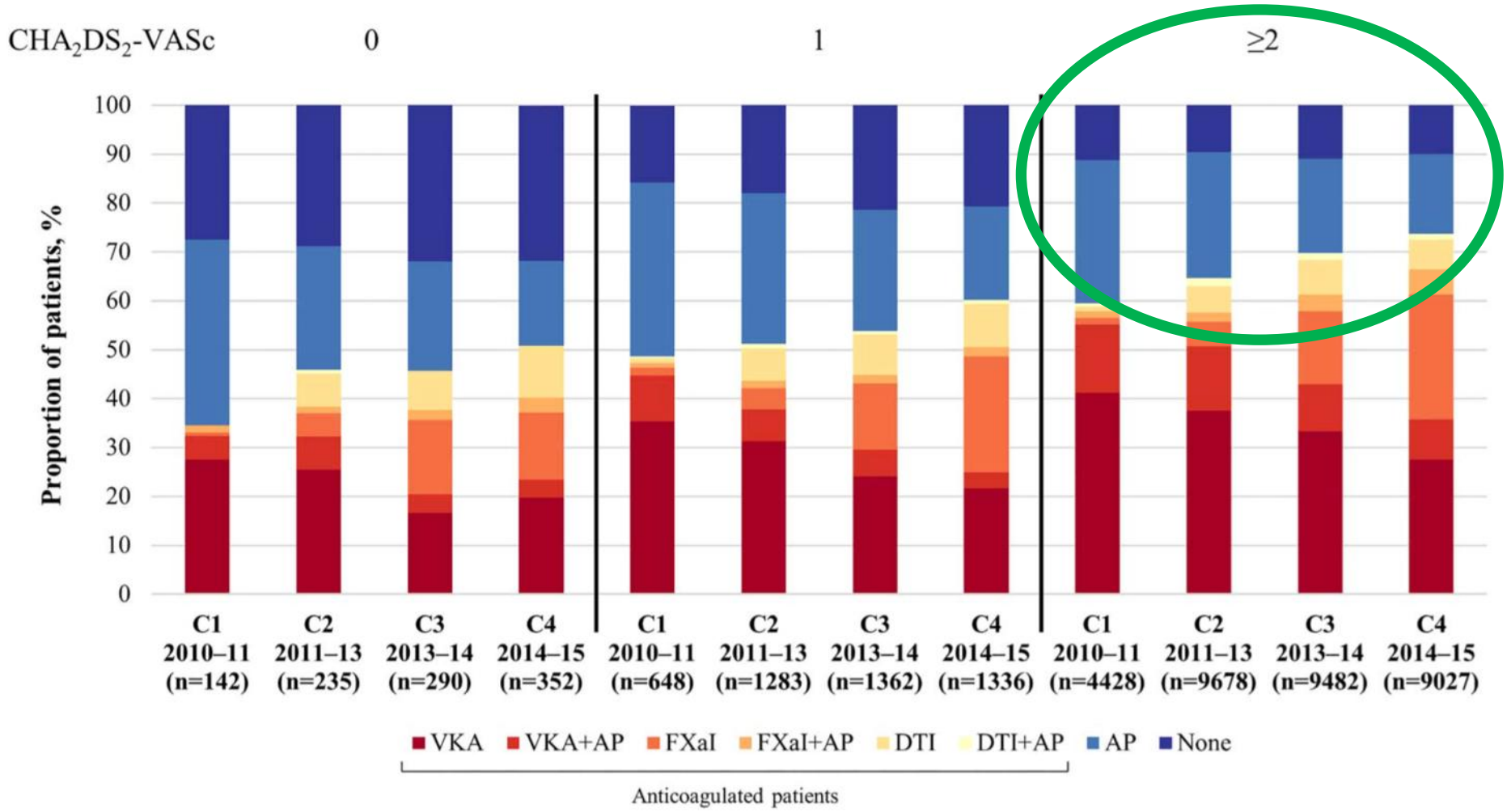


TTR	*P* Value vs No Warfarin
71% to 100%	.03
61% to 70%	.10
51% to 60%	.40
41% to 50%	.73
31% to 40%	.41
<30%	.17
No warfarin	Ref

*Retrospective cohort study conducted using data collected between April 1995 and March 2000 in the United Kingdom from 5513 patients.

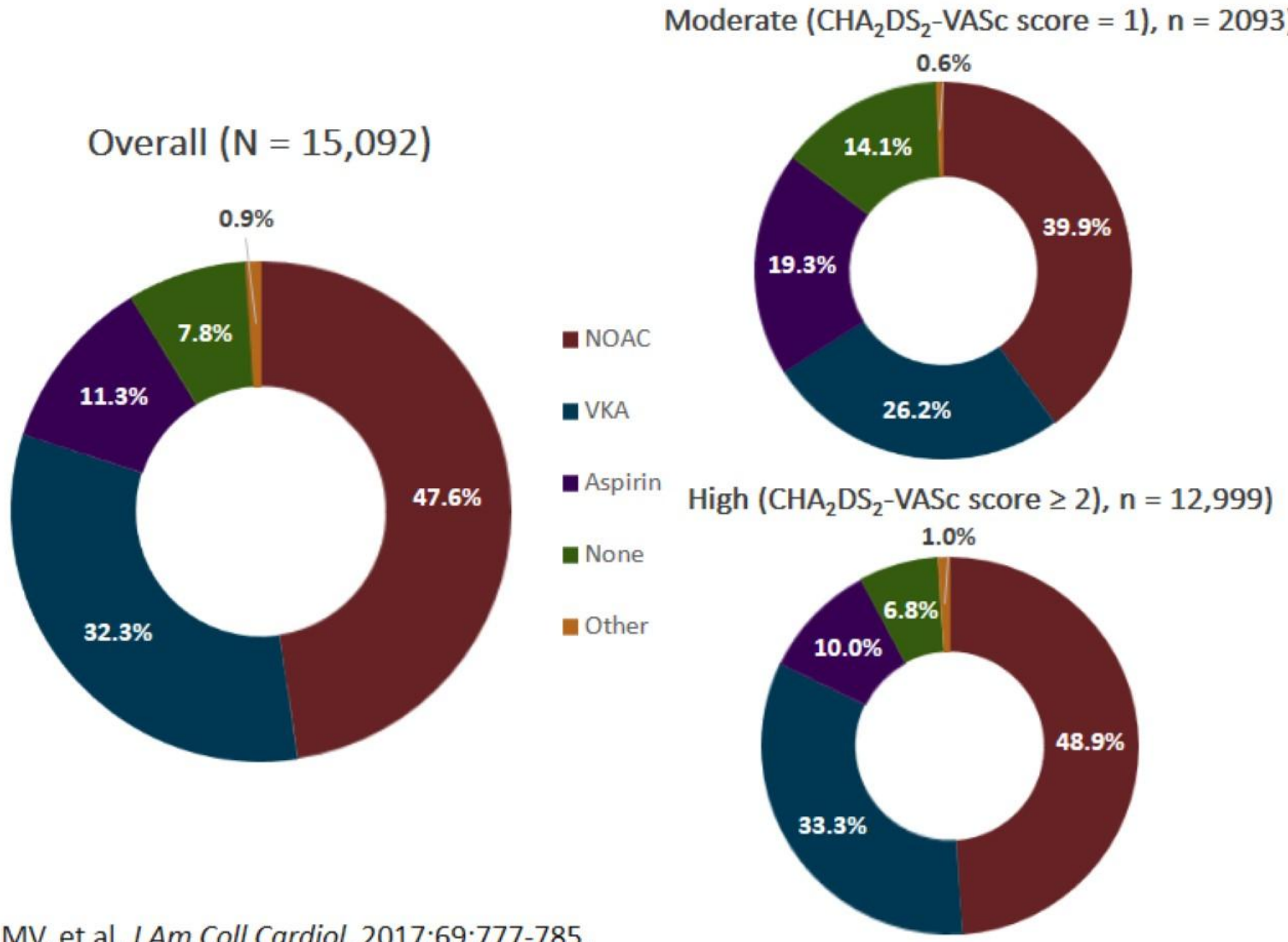
Morgan CL, et al. Thromb Res. 2009;124:37-41.

GARFIELD : Jsme daleko od optima…



Camm AJ, et al. Heart 2016;0:1–8.

GLORIA: Antithrombotic Therapy by CHA_2DS_2-VASc Score



Huisman MV, et al. *J Am Coll Cardiol*. 2017;69:777-785.

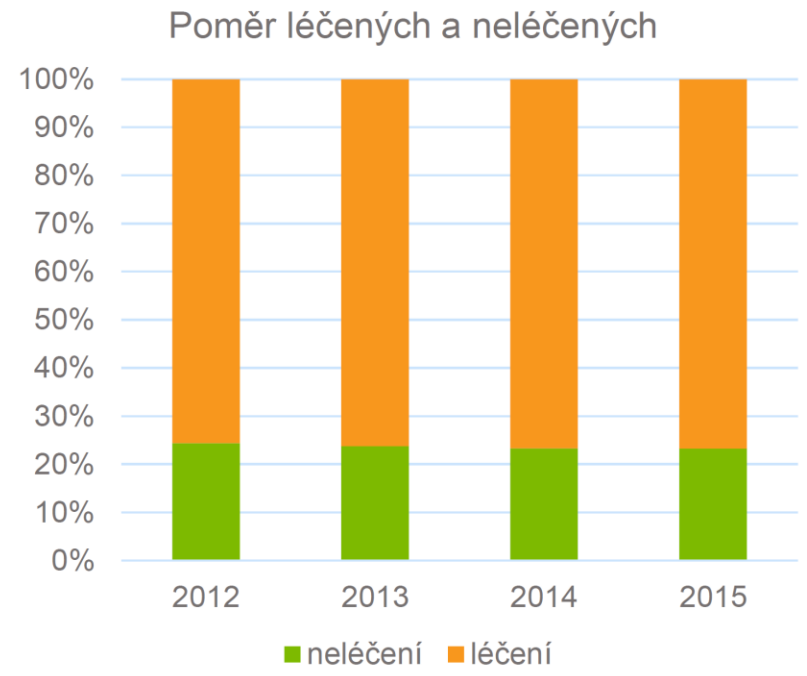
Léčba fibrilace síní v ČR

- Prevalence AF je uváděna na úrovni 1-2 % z celkové populace, tj. 100 – 200 tisíc pacientů (Čihák et al., 2011).
- Celkem je léčeno 324 tisíc pacientů ročně.
- Absolutní počet pacientů s AF narůstá, procento léčených* pacientů je relativně stabilní.

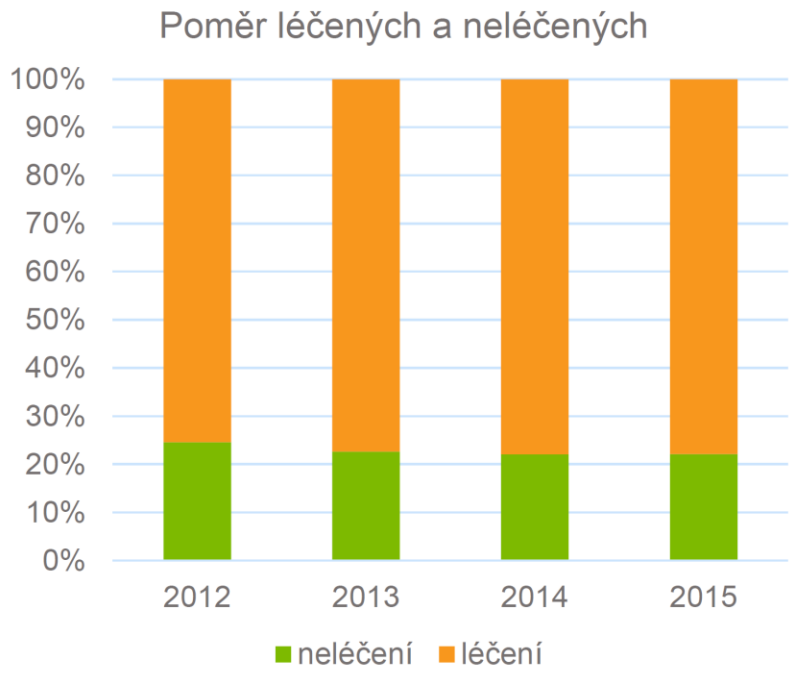
Počet pacientů s dg. AF	2012	2013	2014	2015
Počet pacientů s dg. AF	413 396	461 652	497 745	521 922
Počet léčených pacientů	251 124	281 447	305 884	324 030
% léčených pacientů	60,75%	60,97%	61,45%	62,08%

% léčených pacientů s FS v PP a SP

Primární prevence



Sekundární prevence



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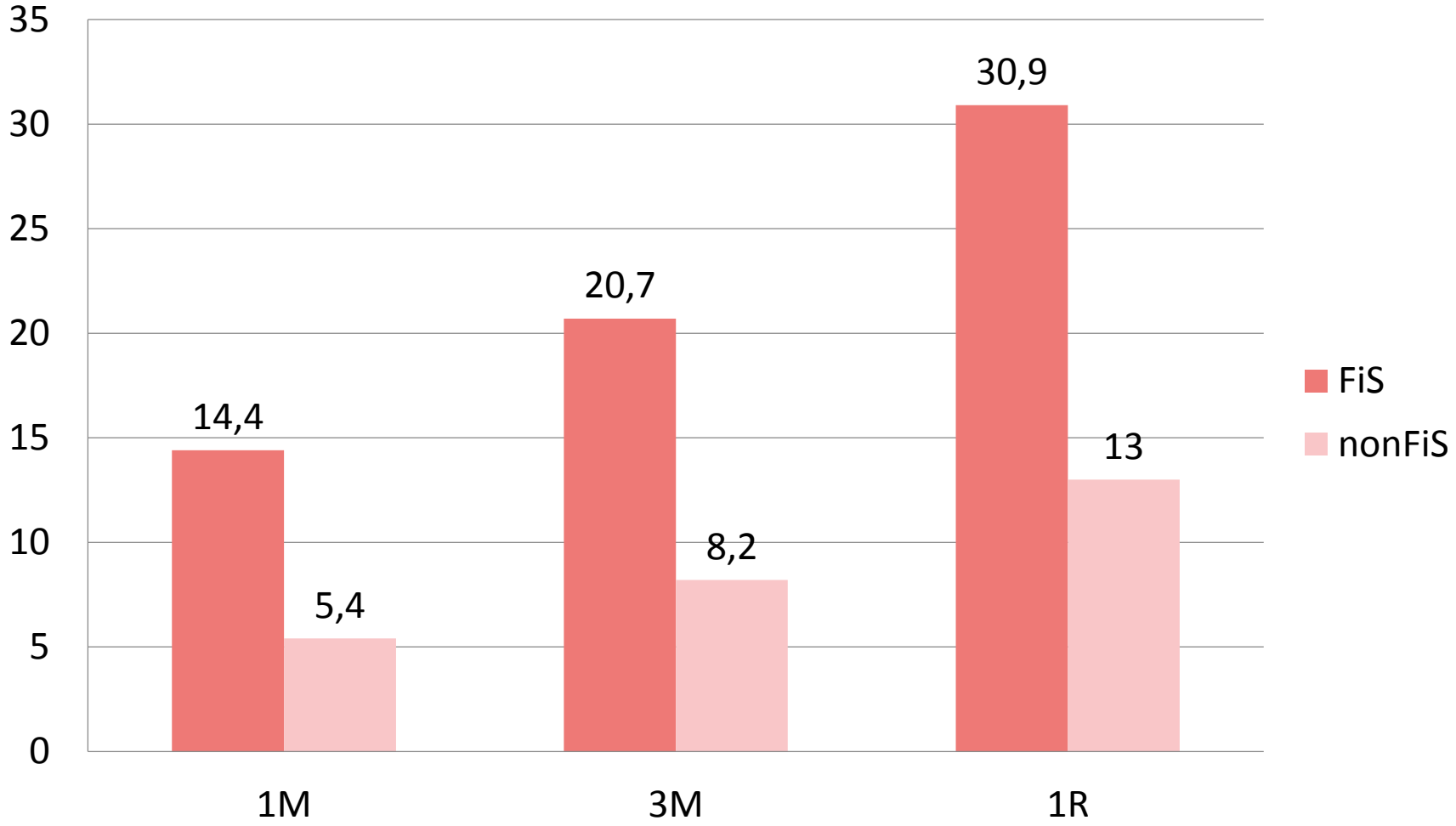
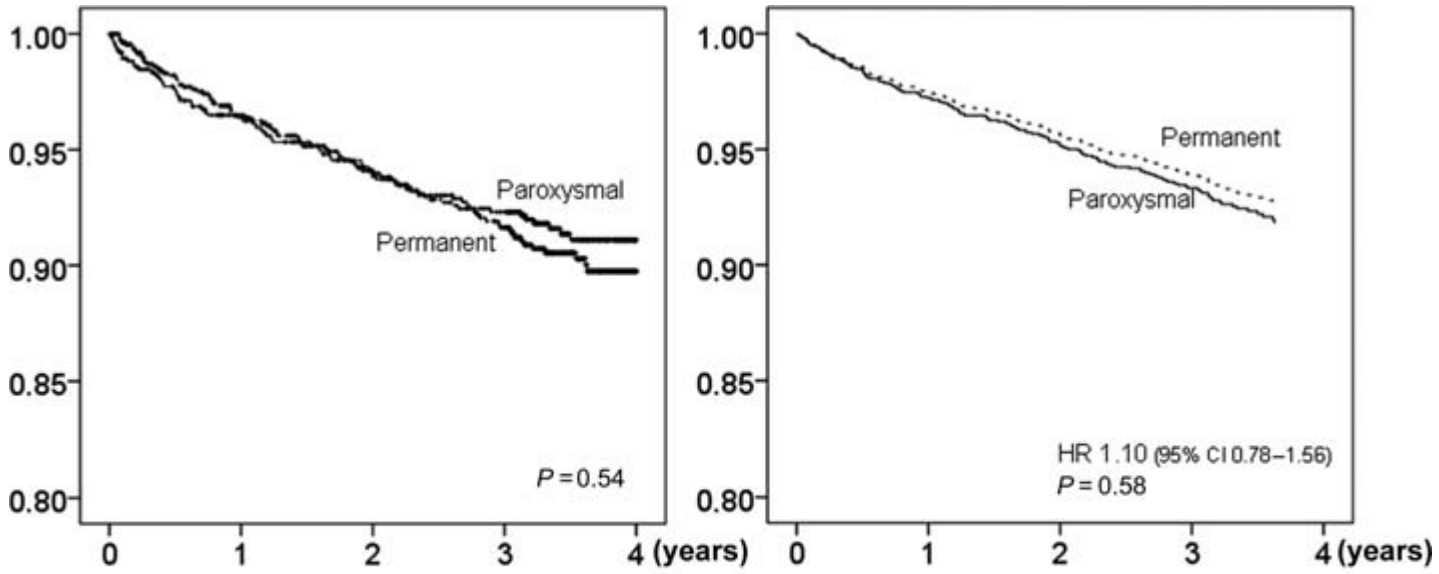
II: FS a CMP: Dva vzájemně patofyziologicky podmíněné světy...

Mortalita první ischemické CMP – etiologie FS ano/ne



Andersen KK et al. Stroke. 2011;42:2806-2812.

Mýtus: Riziko CMP : Paroxyzmální x perzistující FS

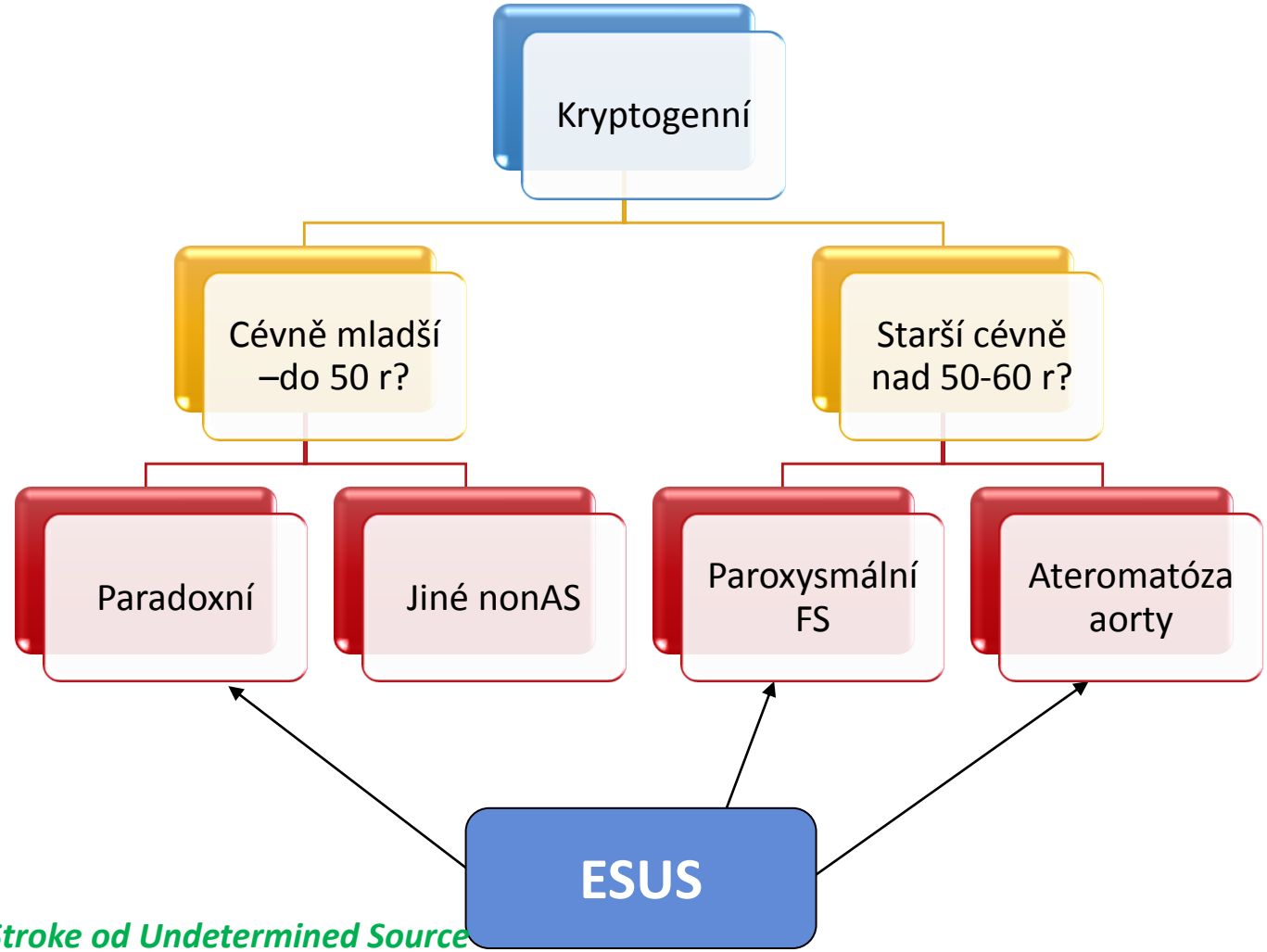


At risk

	Index	1 year	2 years	3 years	4 years
PxAF	855	751	689	630	10
PermAF	1126	910	774	658	29

Friberg L et al. European Heart Journal 2010,31,967-975
doi:10.1093/eurheartj/ehn599

Nová klasifikace: Kryptogenní x ESUS CMP

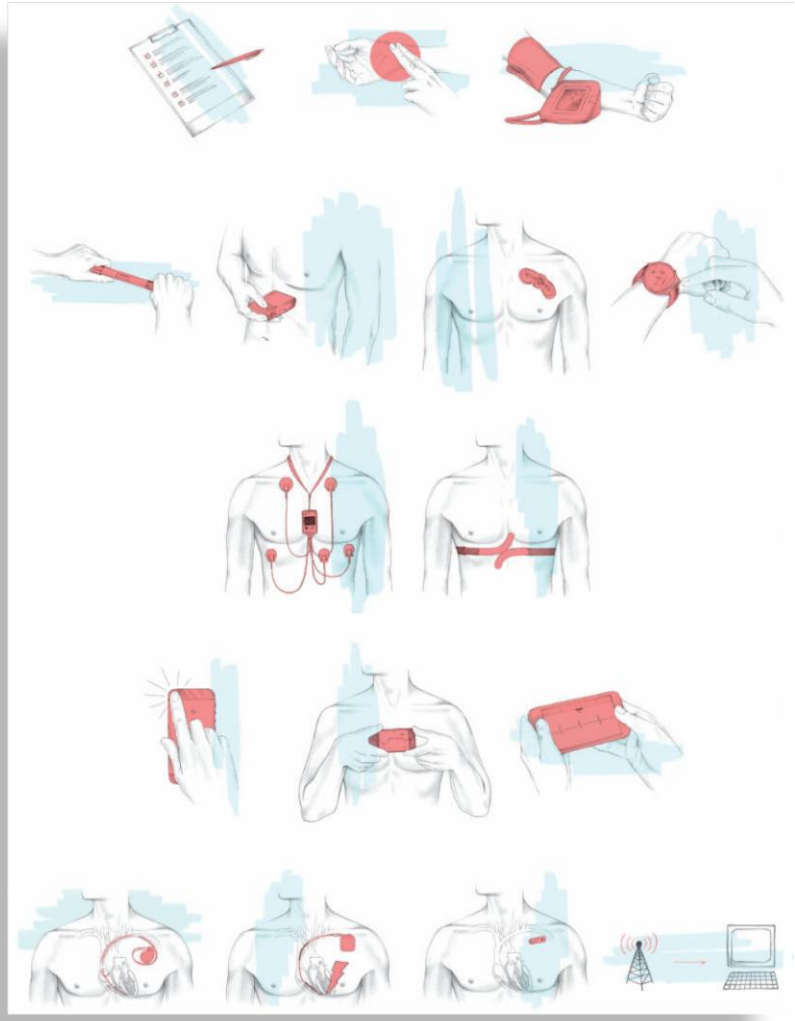


ESUS: Embolic Stroke od Undetermined Source

Hart et al. Lancet Neurology 2014

EHRA CONSENSUS DOCUMENT
Současné možnosti screeningu FS

1. Klinická detekce
2. Jednoelektrodové systémy
3. Víceelektrodové systémy
4. Apps a TM produkty
5. Implantabilní přístroje (AHRE)



Mairesse G H. Europace (2017) 19, 1589–1623 EHRA CONSENSUS DOCUMENT doi:10.1093/europace/eux177

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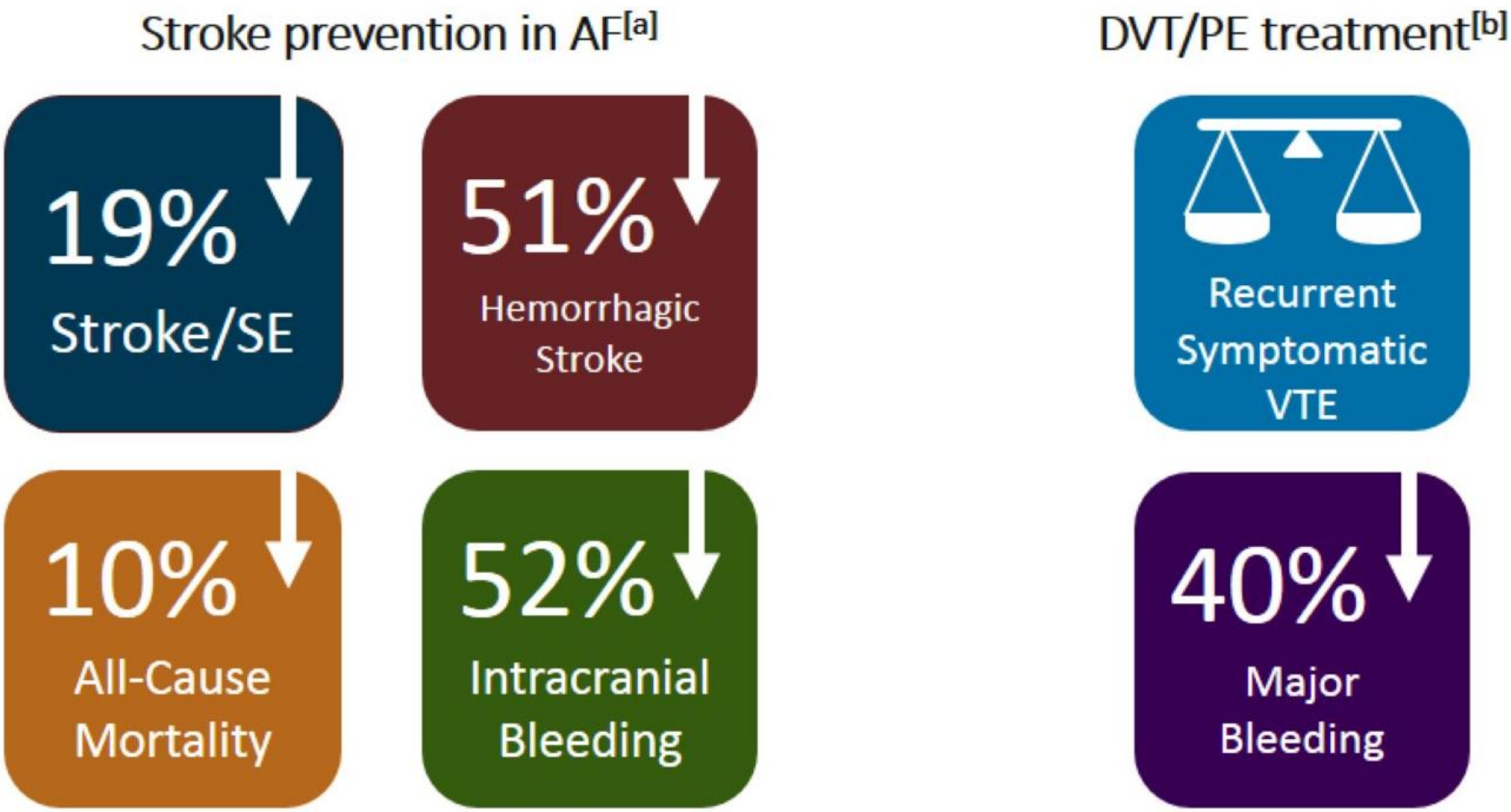
III: NOAC u fragilních pacientů

NOACs demonstrovaly napříč všemi molekulami bezpečnost a efektivitu



a. Ruff C, et al. Lancet. 2014;383:955-962.
b. Hirschl M, et al. Vasa. 2014;43:353-364.

ESC/EHRA Recommendation for Dose Reduction

Cockcroft-Gault formula

$$eCcr = \frac{(140\text{-Age}) \times \text{Mass (in kilograms)} \times (0.85 \text{ if female})}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

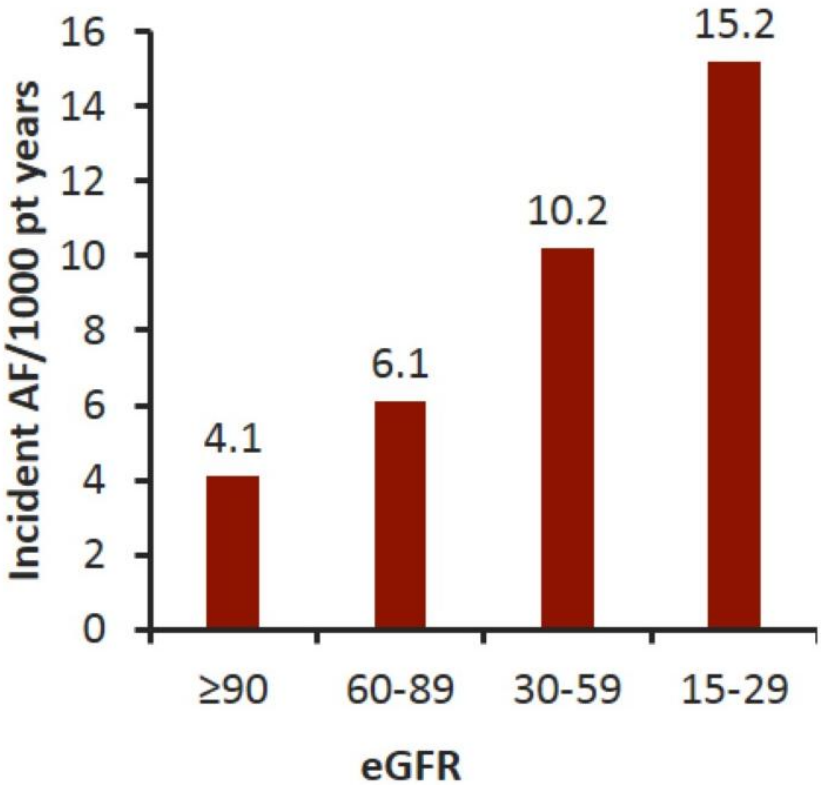
	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Dose adjustments with CKD	None	15 mg once daily if CrCL <30-49 mL/min	2.5 mg twice daily if 2 of the following: serum creatinine ≥ 1.5 mg/dL (133 µmol/L), age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if any of the following: CrCl <50 mL/min, weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone

Cockcroft DW, et al. *Nephron*. 1976;6:31-41.
Kirchhof P, et al. *Eur Heart J.* 2016;37:2893-2962.

Výskyt fibrilace síní u pacientů s chronickou renální insuficiencí

Prevalence of CKD in patients with known AF:

- 28% have eGFR <60
- 10% have eGFR <45



Alonso A. Circulation. 2011;123:2946-2953; Go AS. Circulation. 2009;119:1363-1369.

Risk-Benefit Profile of NOACs vs Warfarin in the Elderly

	Stroke/Systemic Thromboembolism, %/y	
	Age < 75 y	Age > 75 y
RE-LY		
Dabigatran 150 mg	0.9	1.4
Warfarin	1.4	2.1
ROCKET-AF		
Rivaroxaban	2	2.3
Warfarin	2.1	2.9
ARISTOTLE		
Apixaban	1.2	1.6
Warfarin	1.7	2.2
ENGAGE-TIMI 48		
Edoxaban -- higher dose	1.7	1.9
Warfarin	1.8	2.3

Turagam MK, et al. *Clin Interv Aging*. 2015;10:1431-1444.

NOAC Administration: With or Without Food

Apixaban	Can be taken with or without food
Dabigatran	Yes -- may lessen risk of dyspepsia
Edoxaban	Can be taken with or without food
Rivaroxaban	Yes -- should be taken with a meal

- Requirement to take with food might have a negative influence on adherence

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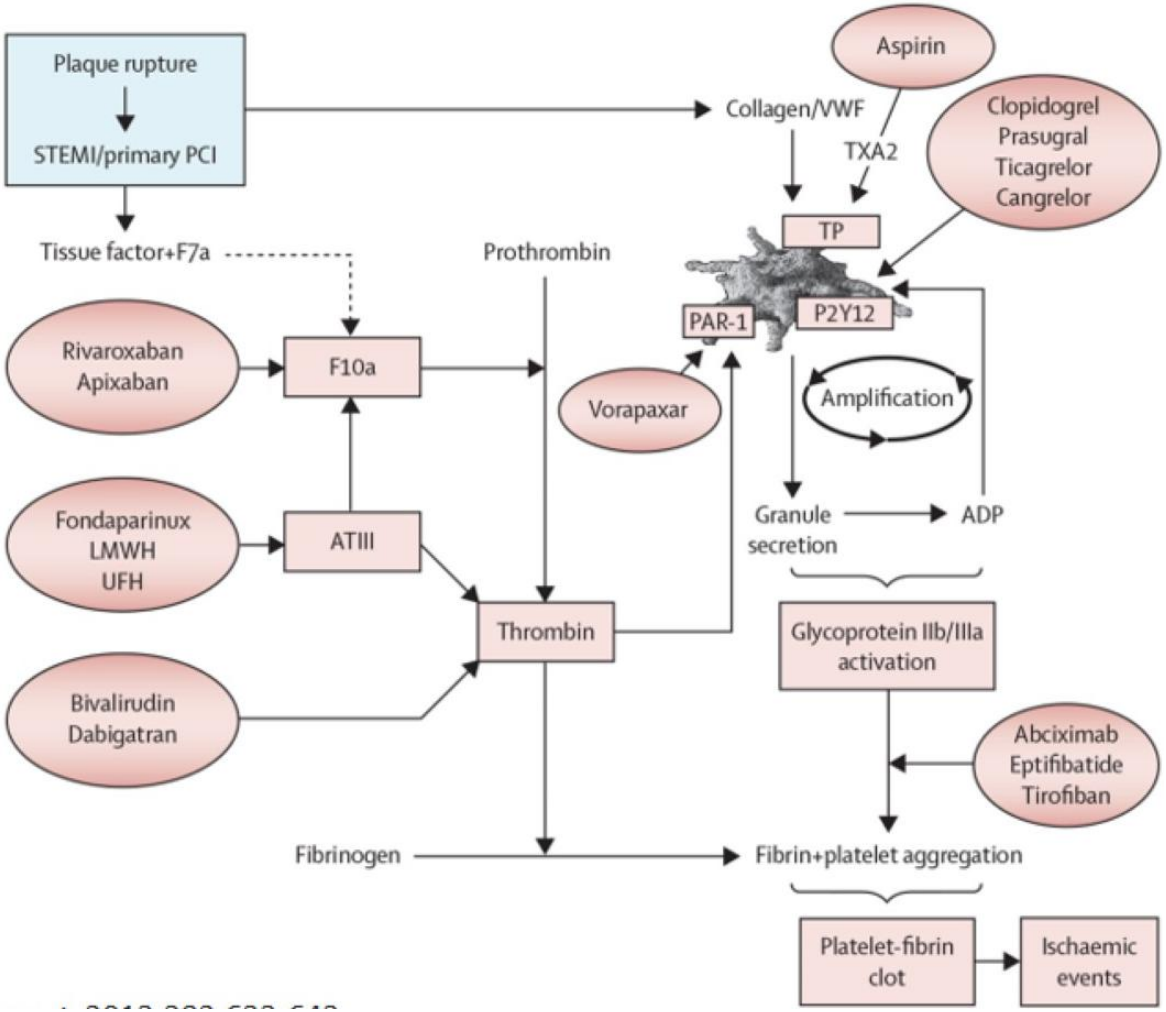
IV: Máme v současné době dostatek důkazů o bezpečnosti a efektivitě NOACs u pacientů s ICHS a PCI ?

Instabilní plát u pacientů s akutním koronárním syndromem podstupujícím PCI



Curzen N, et al. Lancet. 2013;382:633-643.

Platelet -- All Trials

	RE-LY			ROCKET-AF		ARISTOTLE		ENGAGE AF-TIMI 48			Combined	
	Dabigatran 150 mg (n = 6076)	Dabigatran 110 mg (n = 6015)	Warfarin (n = 6022)	Rovaroxaban (n = 7131)	Warfarin (n = 7133)	Apixaban (n = 9120)	Warfarin (n = 9081)	Edoxaban 60 mg (n = 7035)	Edoxaban 30 mg (n = 7034)	Warfarin (n = 7036)	NOAC (n = 42,411)	Warfarin (n = 29,272)
Aspirin at baseline, %	39	40	41	36	37	31	31	29	29	30	34	34

Ruff CT, et al. *Lancet.* 2014;383:955-962.

Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography

S. Kralev[1], K. Schneider[1], S. Lang[1], T. Süselbeck[1], M. Borggrefe[1]

(1) University Medical centre Mannheim, Mannheim, Germany

Introduction:

In standard reference sources the incidence of coronary artery disease (CAD) in patients with atrial fibrillation (AF) ranged between 24 and 46.5%. Since then the incidence of cardiovascular risk factors and CAD has dramatically increased and this trend is projected to continue. Newer studies report different incidences of CAD in patients with AF but also focus on different patient groups, so data is lacking on the overall incidence of CAD in AF patients in the modern era of cardiology. Modern treatment strategies (single oral bolus dose of flecainide and propafenone – "pill in the pocket") are only applicable to patients without structural heart disease. It was the purpose of this study to investigate the overall incidence and severity of CAD in patients with AF.

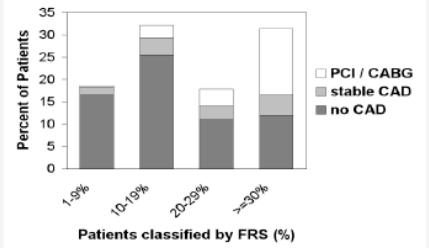
Methods:

From January 2005 until December 2009 we included 261 consecutive patients admitted to hospital with paroxysmal, persistent or permanent AF in this prospective study. Independent of the rhythm on admission, patients with previously known AF as well as patients with diagnosed AF on admission were included. Patients with previously diagnosed or previously excluded CAD, acute coronary syndromes and dilated or hypertrophic cardiomyopathy were excluded All patients underwent coronary angiography and the Framingham risc score (FRS) was calculated.

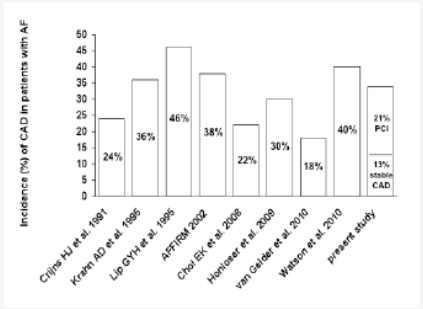
Table 1. Comparison of patients without CAD and patients with CAD

Patient characteristic	Without CAD (n =171)	With CAD (n =90)	P-Value
Age ± SD (Years)	68 ± 10	73 ± 8	**0.001**
Male sex	102 [60%]	65 [72%]	0.057
Type of AF			
Paroxysmal	77 [45%]	47 [52%]	0.30
Persistent	47 [27%]	16 [18%]	0.095
Permanent	47 [27%]	27 [30%]	0.67
Risk factors			
Smoking	23 [13%]	23 [26%]	**0.017**
Hypercholesterolemia	52 [30%]	54 [60%]	**< 0.001**
Hypertension	113 [66%]	65 [72%]	0.33
Obesity	38 [22%]	20 [22%]	1.0
Familiar history of CAD	16 [9%]	9 [10%]	0.83
Diabetes mellitus	25 [15%]	21 [23%]	0.11
Left ventricular systolic function*			
EF ≥ 55 %	119 [70%]	52 [58%]	0.075
EF 45-54 %	34 [20%]	22 [24%]	0.43
EF 30-44 %	12 [7%]	11 [12%]	0.17
EF < 30 %	6 [4%]	5 [6%]	0.52
Other data			
Angina pectoris	3 [2%]	33 [37%]	**< 0.001**
Above-average alcohol consumption	5 [3%]	2 [2%]	1.0
Hyperthyreosis	14 [8%]	14 [16%]	0.091
Medication at discharge			
Aspirin	24 [14%]	47 [52%]	**< 0.001**
Clopidogrel	3 [2%]	39 [43%]	**< 0.001**
Phenprocoumon	119 [70%]	32 [36%]	**< 0.001**
Beta-Blockers	118 [69%]	62 [69%]	1.0
Calcium channel antagonists	26 [15%]	17 [19%]	0.48
Digitalis glycosides	71 [42%]	44 [49%]	0.29
Amiodarone	7 [4%]	2 [2%]	0.72
Flecainide	23 [13%]	5 [6%]	0.059
Propafenone	16 [9%]	1 [1%]	**0.008**

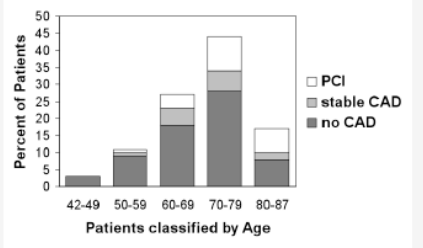
AF = Atrial Fibrillation, CAD = Coronary Artery Disease, EF = Ejection Fraction, SD = Standard Deviation, *Significant "within group" trend towards EF ≥ 55%.



Significant linear trend among the FRS categories in % and the prevalence of CAD and PCI/CABG (p<0.0001). Legend: CABG = Coronary Artery Bypass Graft, CAD = Coronary Artery Disease, FRS = Framingham risk score, PCI = Percutaneous Coronary Intervention



Overview of reported incidences of coronary artery disease in patients presenting with atrial fibrillation. Legend: AF = Atrial Fibrillation, CAD = Coronary Artery Disease, PCI = Percutaneous Coronary Intervention.



Incidence and severity of coronary artery disease in patients presenting with atrial fibrillation according to age. Legend: CAD = Coronary Artery Disease, PCI = Percutaneous Coronary Intervention

Results:

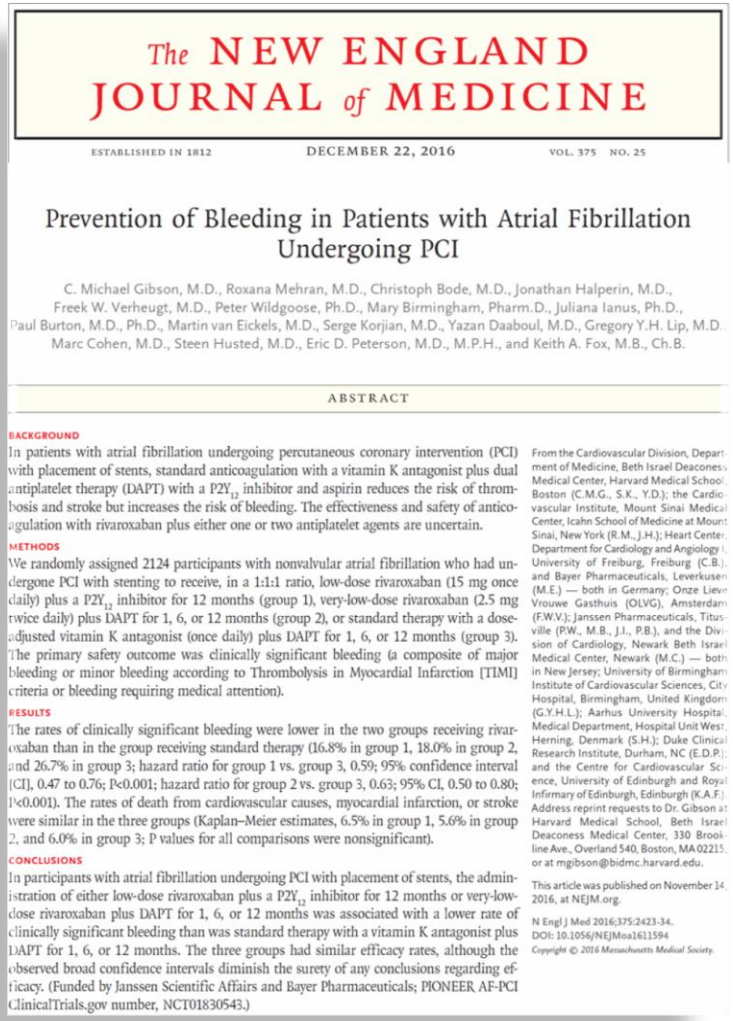
The overall incidence of CAD in patients presenting with AF was 34%, in patients >70 years, the incidence of CAD was 41%, the incidence of patients undergoing PCI was 21%. Patients with CAD were older (73±8 years vs 68±10 years, p=0.001), had significantly more frequent hypercholesterolemia (60% vs 30%, p<0.001), were more frequent smokers (26% vs 13%, p=0.017) and suffered from angina more often (37% vs 2%, p<0.001). Patients with stable CAD presented more often with one-vessel disease (79% vs 34%, p<0.0001). There was a significant linear trend among the FRS categories in % and the prevalence of CAD and PCI/CABG (p<0.0001) with more cases of PCI and CAD at elevated FRS levels. A therapy with a class Ic antiarrhythmic drug was initiated in 39 of 171 patients (23%).

Conclusions:

The overall incidence of CAD in patients presenting with AF was 34%, the incidence of patients undergoing PCI was 21%.

Based upon increasing CRF in the western world, we recommend a careful investigation respecting the FRS to either definitely exclude, or establish an early diagnosis of CAD - which could be contributing to an early and safe therapeutic strategy considering type Ic antiarrhythmic drugs and oral anticoagulation.

Ano, máme dostatek důkazů a novinky…



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

ABSTRACT

BACKGROUND

In patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) with placement of stents, standard anticoagulation with a vitamin K antagonist plus dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin reduces the risk of thrombosis and stroke but increases the risk of bleeding. The effectiveness and safety of anticoagulation with rivaroxaban plus either one or two antiplatelet agents are uncertain.

METHODS

We randomly assigned 2124 participants with nonvalvular atrial fibrillation who had undergone PCI with stenting to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2), or standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (group 3). The primary safety outcome was clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention).

RESULTS

The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% confidence interval [CI], 0.47 to 0.76; P<0.001; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; P<0.001). The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups (Kaplan–Meier estimates, 6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were nonsignificant).

CONCLUSIONS

In participants with atrial fibrillation undergoing PCI with placement of stents, the administration of either low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy. (Funded by Janssen Scientific Affairs and Bayer Pharmaceuticals; PIONEER AF-PCI ClinicalTrials.gov number, NCT01830543.)

From the Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (C.M.G., S.K., Y.D.); the Cardiovascular Institute, Mount Sinai Medical Center, Icahn School of Medicine at Mount Sinai, New York (R.M., J.H.); Heart Center, Department for Cardiology and Angiology I, University of Freiburg, Freiburg (C.B.), and Bayer Pharmaceuticals, Leverkusen (M.E.) — both in Germany; Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam (F.W.V.); Janssen Pharmaceuticals, Titusville (P.W., M.B., J.I., P.B.), and the Division of Cardiology, Newark Beth Israel Medical Center, Newark (M.C.) — both in New Jersey; University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.); Aarhus University Hospital, Medical Department, Hospital Unit West, Herning, Denmark (S.H.); Duke Clinical Research Institute, Durham, NC (E.D.P.); and the Centre for Cardiovascular Science, University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh (K.A.F.). Address reprint requests to Dr. Gibson at Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Overland 540, Boston, MA 02215, or at mgibson@bidmc.harvard.edu.

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DOI: 10.1056/NEJMoa1611594

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Triple antithrombotic therapy with warfarin plus two antiplatelet agents is the standard of care after percutaneous coronary intervention (PCI) for patients with atrial fibrillation, but this therapy is associated with a high risk of bleeding.

METHODS

In this multicenter trial, we randomly assigned 2725 patients with atrial fibrillation who had undergone PCI to triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). Outside the United States, elderly patients (≥80 years of age; ≥70 years of age in Japan) were randomly assigned to the 110-mg dual-therapy group or the triple-therapy group. The primary end point was a major or clinically relevant nonmajor bleeding event during follow-up (mean follow-up, 14 months). The trial also tested for the noninferiority of dual therapy with dabigatran (both doses combined) to triple therapy with warfarin with respect to the incidence of a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization.

RESULTS

The incidence of the primary end point was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63; P<0.001 for noninferiority; P<0.001 for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; P<0.001 for noninferiority). The incidence of the composite efficacy end point was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for noninferiority). The rate of serious adverse events did not differ significantly among the groups.

CONCLUSIONS

Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. (Funded by Boehringer Ingelheim; RE-DUAL PCI ClinicalTrials.gov number, NCT02164864.)

Gibson M et al. N Engl J Med 2016;375:2423-34. DOI: 10.1056/NEJMoa1611594
Cannon Ch et al. N Engl J Med, published on August 27, 2017. DOI: 10.1056/NEJMoa1708454

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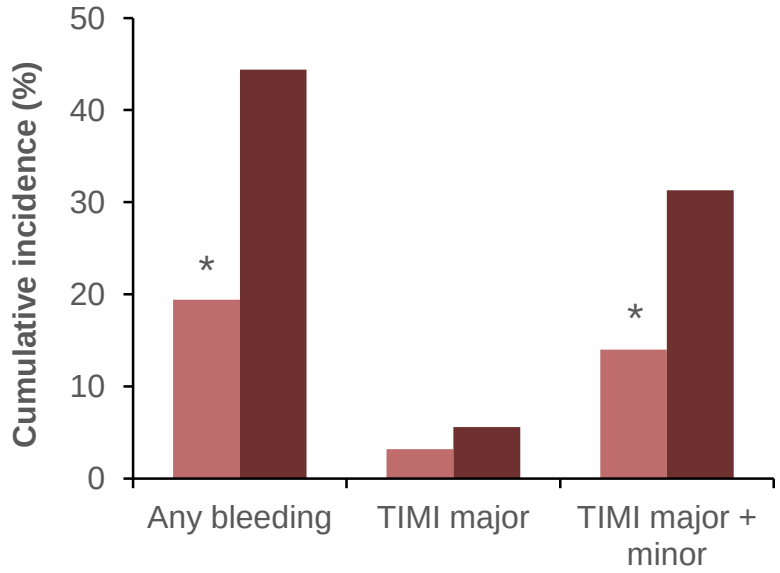
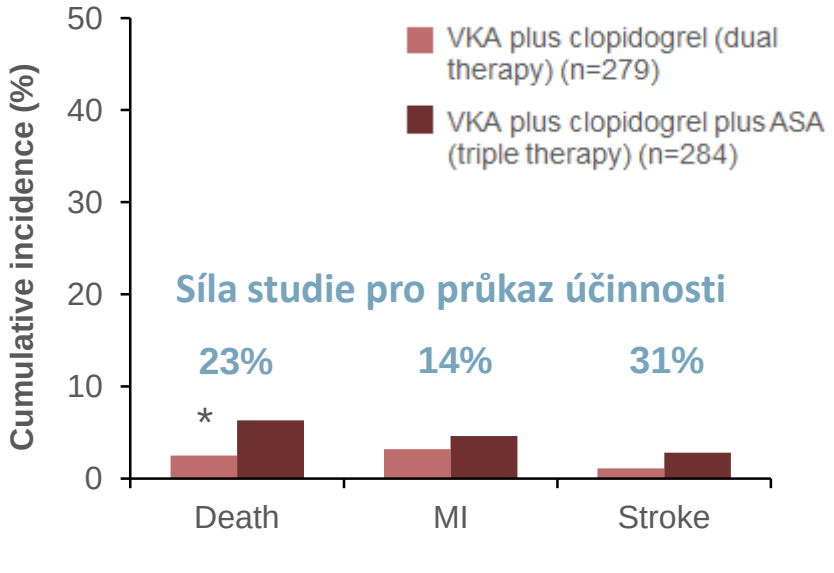
Studie WOEST: Je nezbytná triple terapie s ASA?

Studie malého měřítka, otevřená (N=573) srovnávající bezpečnostní výsledky triple terapie (VKA plus clopidogrel plus ASA) vs duální terapie (VKA plus clopidogrel): **69 % pacientů ve studii WOEST mělo AF.**

Výsledky bezpečnosti



Výsledky účinnosti



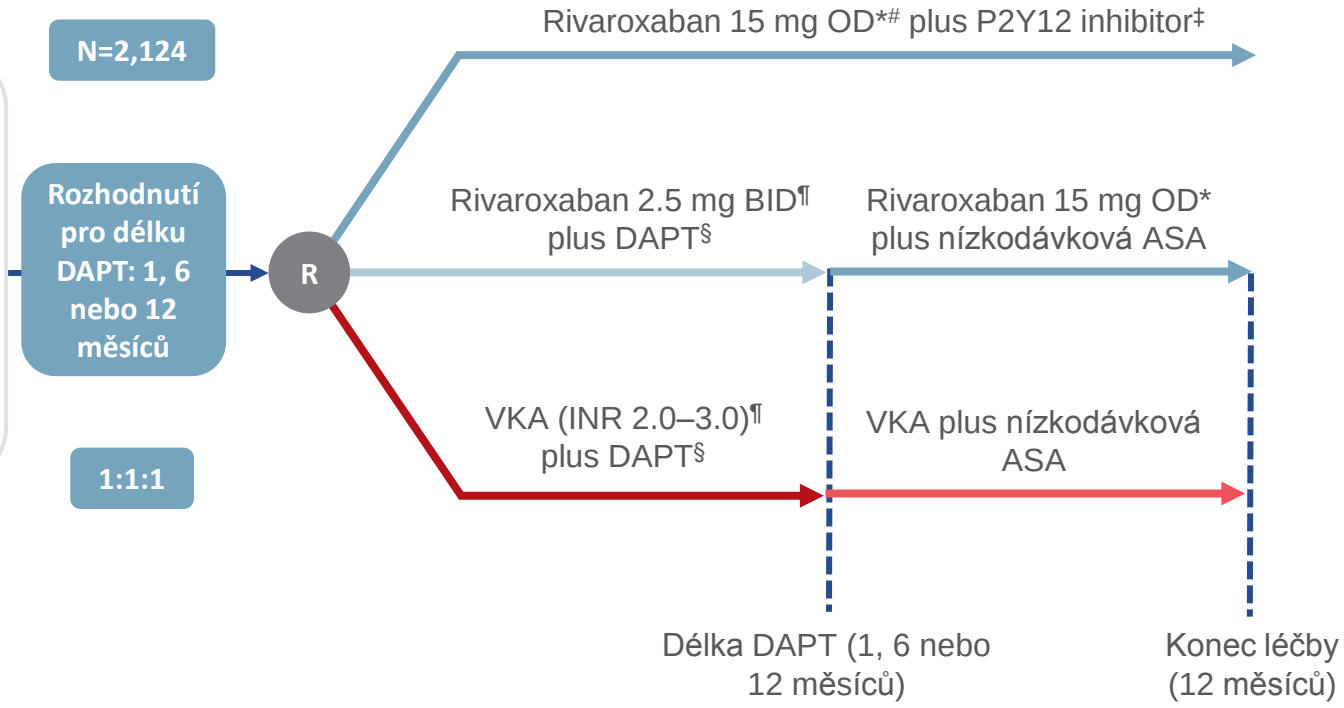
Duální terapie byla spojena se signifikantně nižším výskytem krvácení a celkovou mortalitou ve srovnání s triple terapií při podobném výskytu trombotických příhod.

**p<0.05*
Dewilde WJ et al, Lancet 2013;381:1107–1115

Design studie PIONEER AF PCI

Design: Otevřená, randomizovaná, kontrolovaná bezpečnostní studie fáze IIIb

Populace: pacienti s paroxysmální, persistentní nebo permanentní FS podstupující PCI s implantací stentu



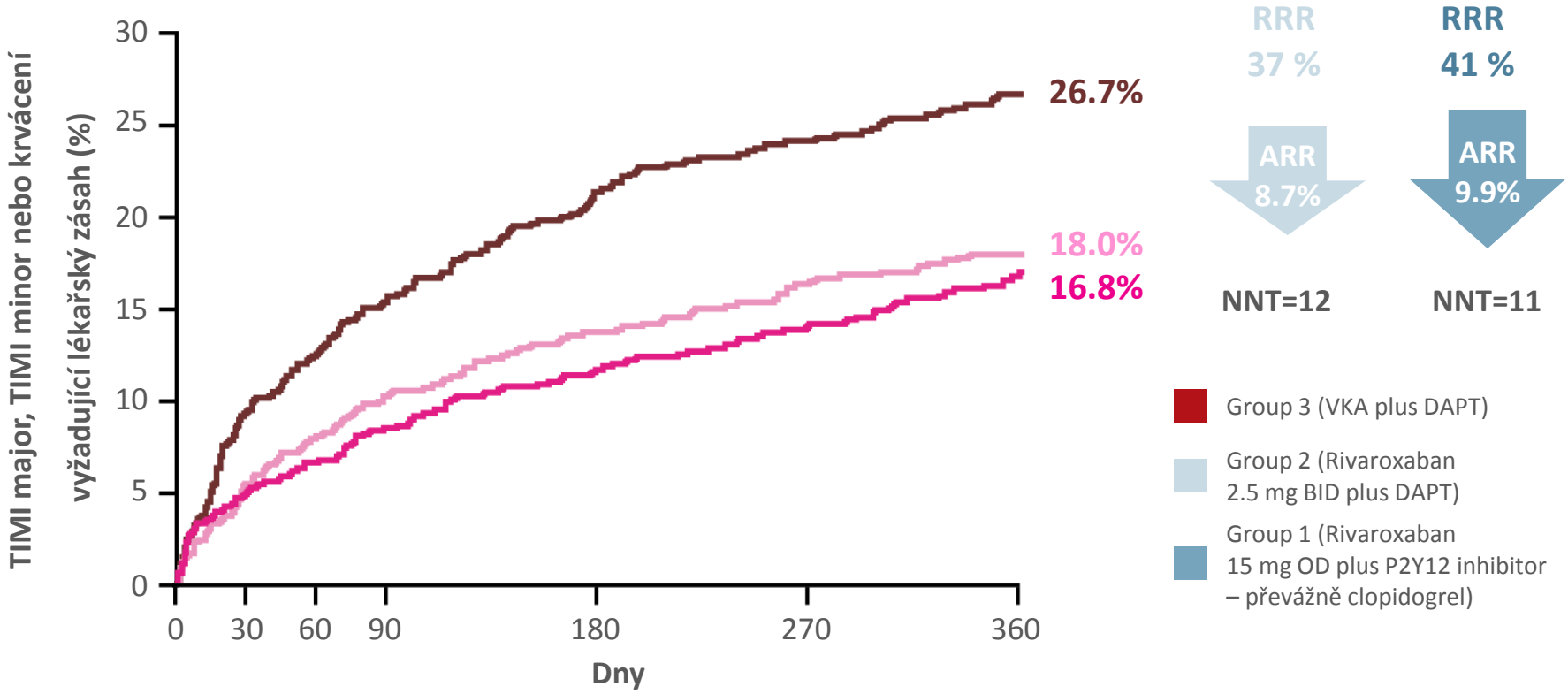
*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡**clopidogrel (75 mg daily)** (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §**ASA (75–100 mg daily) plus clopidogrel (75 mg daily)** (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–96 hours after sheath removal

1. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016]; 2. Gibson CM et al, Am Heart J 2015;169:472–478e5; 3. Gibson CM et al, New Engl J Med 2016; doi: 10.1056/NEJMoa1611594

Obě strategie prokázaly významné zlepšení v parametru bezpečnosti léčby

Rivaroxaban 15 mg OD plus P2Y12 inhibitor (převážně clopidogrel) vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001



Gibson CM et al, New Engl J Med 2016; doi: 10.1056/NEJMoa1611594

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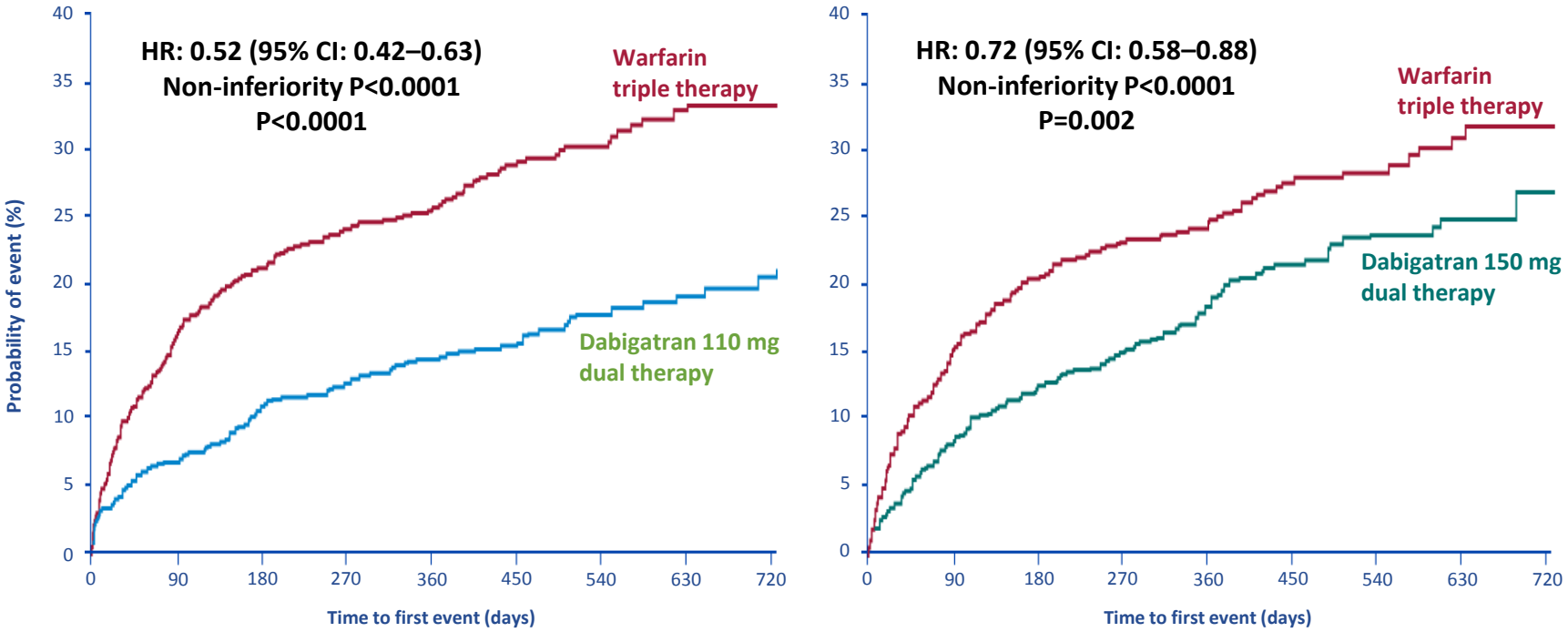
REDUAL-PCI Study

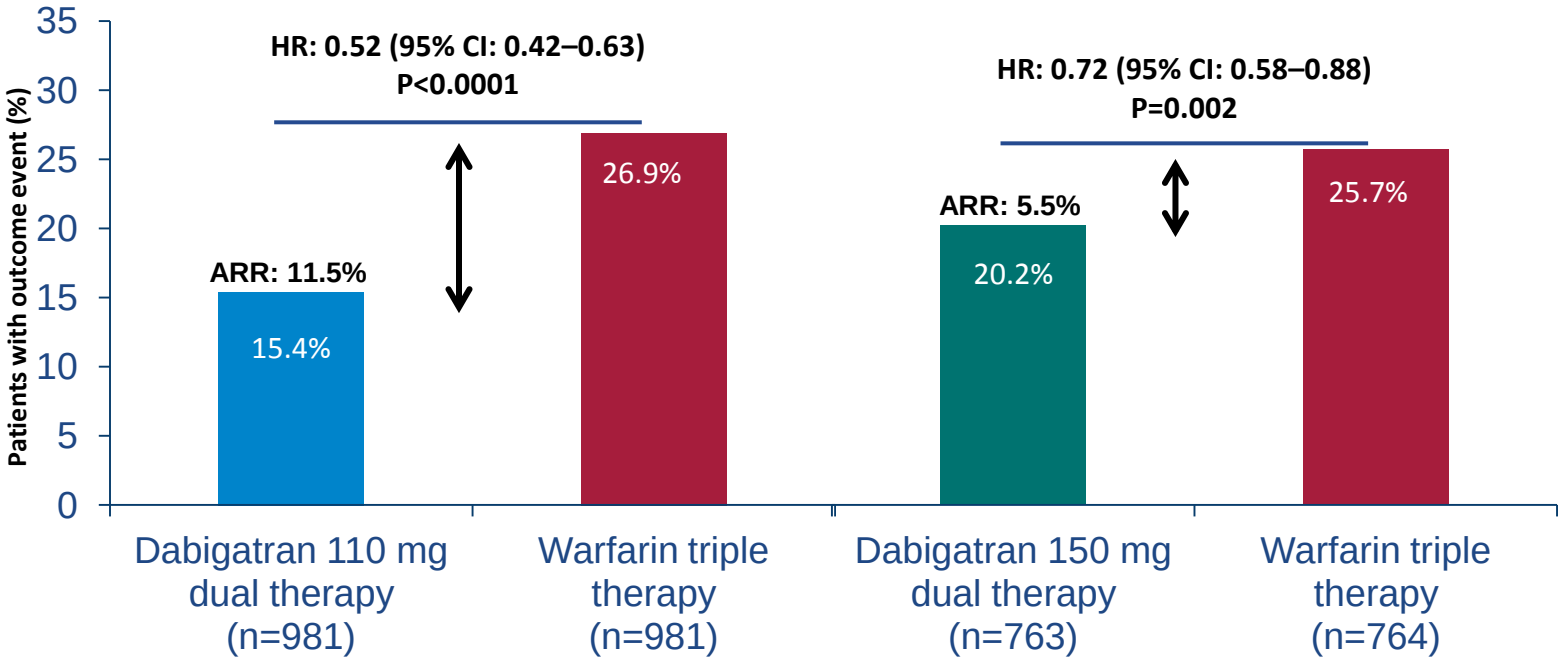
RE-DUAL PCI: Dual antithrombotic therapy with dabigatran after percutaneous coronary intervention in patients with atrial fibrillation

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event



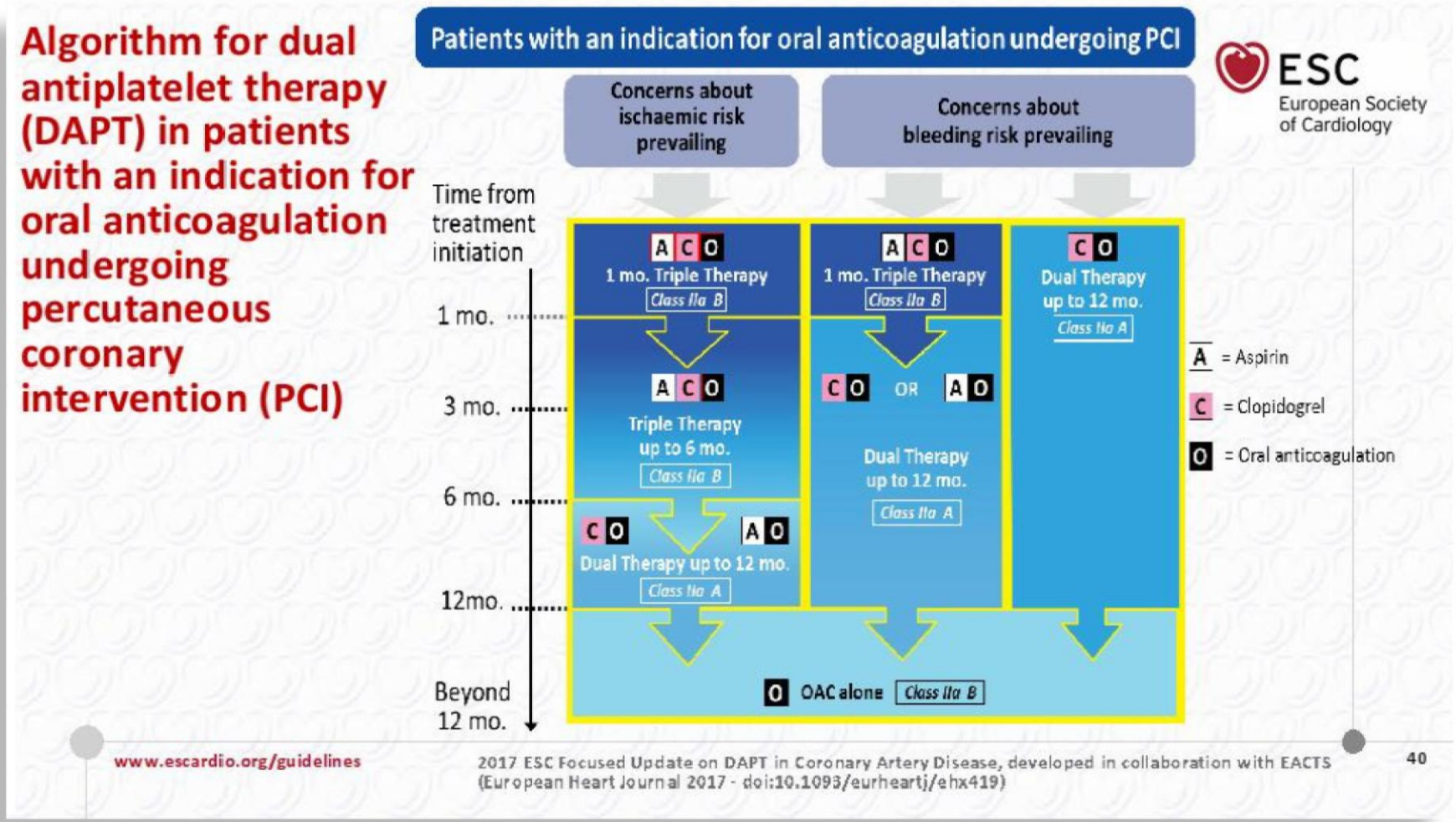
Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Primary endpoint: ISTH major or clinically relevant non-major bleeding event



Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). ARR, absolute risk reduction

DAPT guidelines ESC 2017: ICHS, FS a PCI



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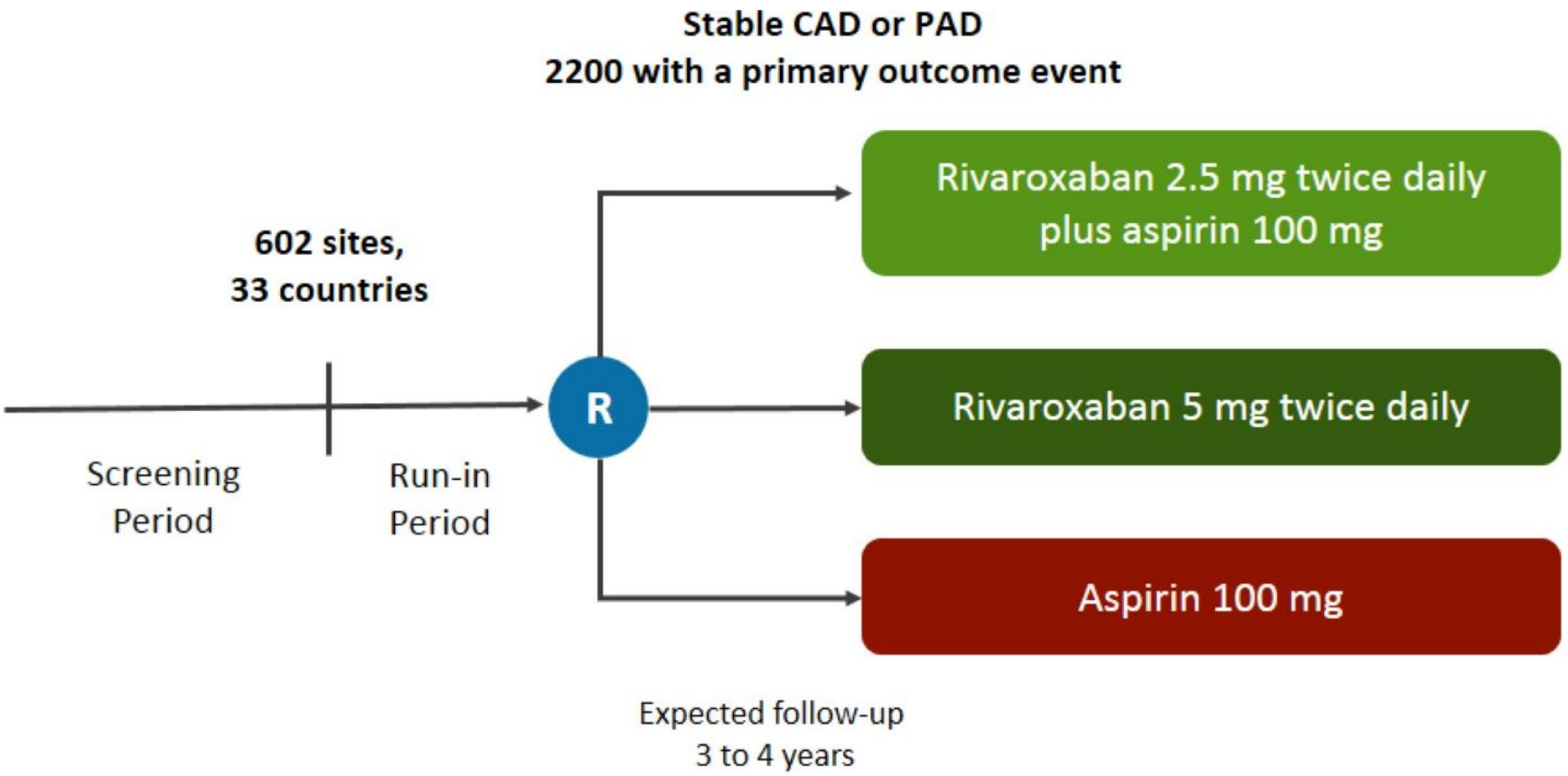
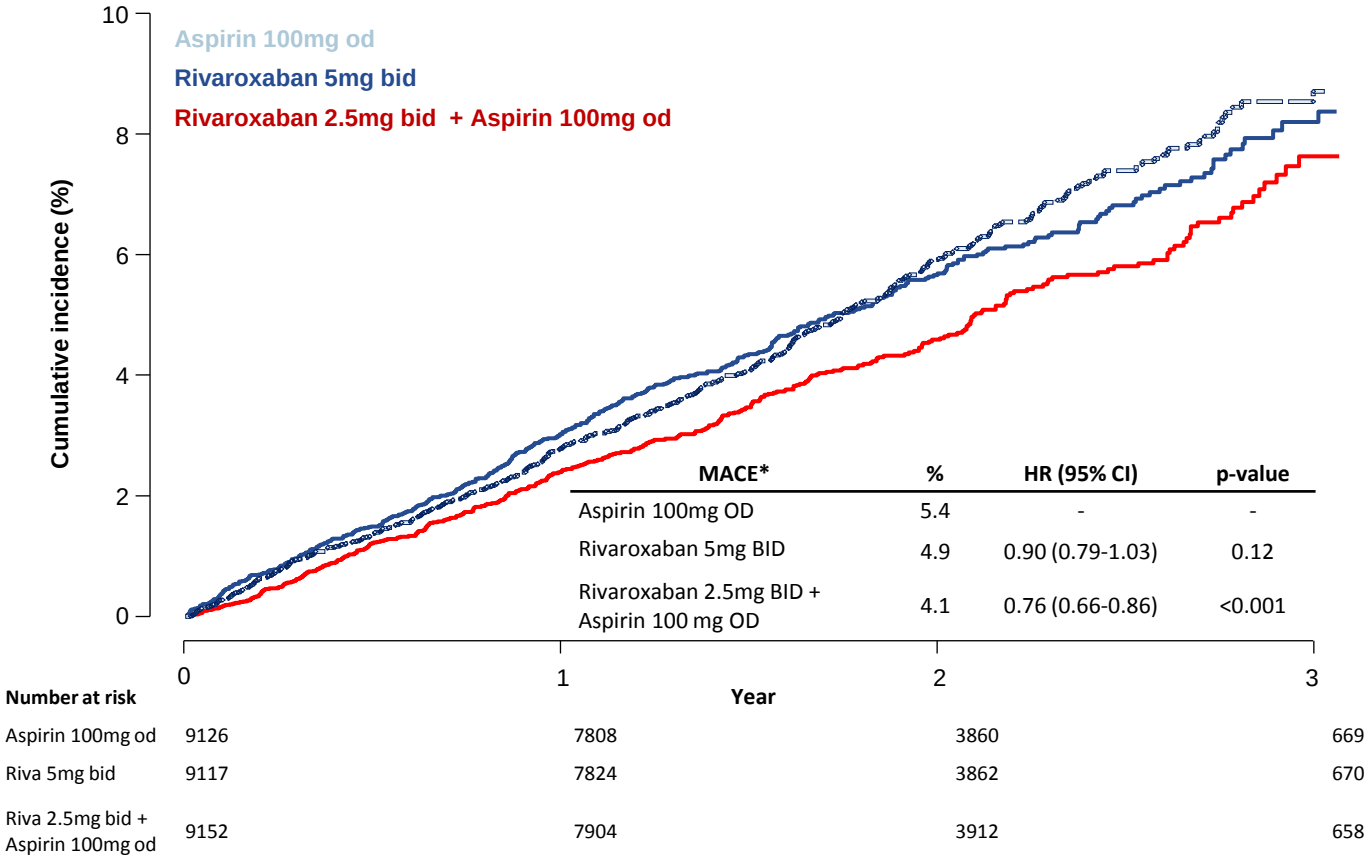
V: Stabilní ICHS/ateroskleróza a antitrombotická terapie

Design studie Compass



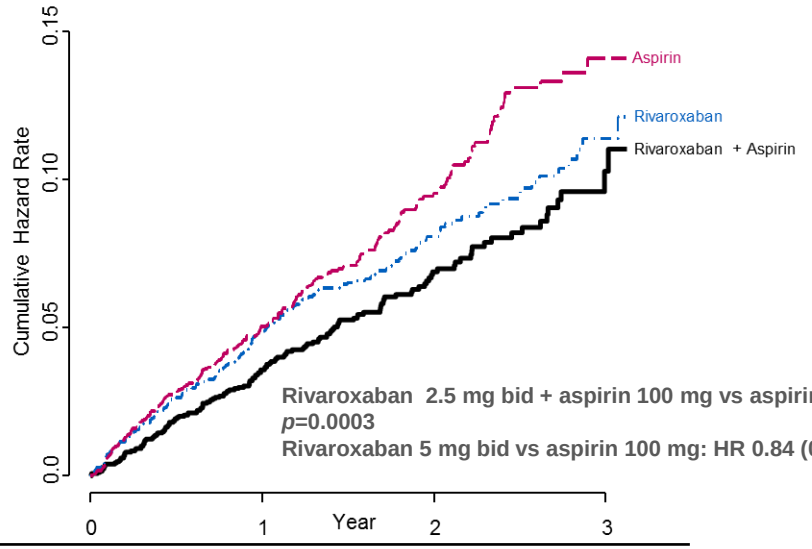
Bosch J, et al. Can J Cardiol. 2017;33:1027-1035; Clinicaltrials.gov NCT01776424

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



**Rates as at mean follow up of 23 months*
Eikelboom JW et al. N Engl J Med 2017; DOI: 10.1056/NEJMoa1709118

31% RRR in MACE or MALE Including Major Amputation with Rivaroxaban 2.5 mg bid + Aspirin Versus Aspirin in Patients with PAD



Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg: HR 0.69 (0.56–0.85), *p*=0.0003
Rivaroxaban 5 mg bid vs aspirin 100 mg: HR 0.84 (0.69–1.02), *p*=0.08

Number at risk				
Rivaroxaban + aspirin	2492	2069	893	124
Rivaroxaban	2474	2023	864	147
Aspirin	2504	2034	911	113

COMPASS

Anand SS et al. ESC 2017, Abs 1157; Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1220&sessId=22247&subSessId=0;
Anand SS et al. Lancet 2017;In Press

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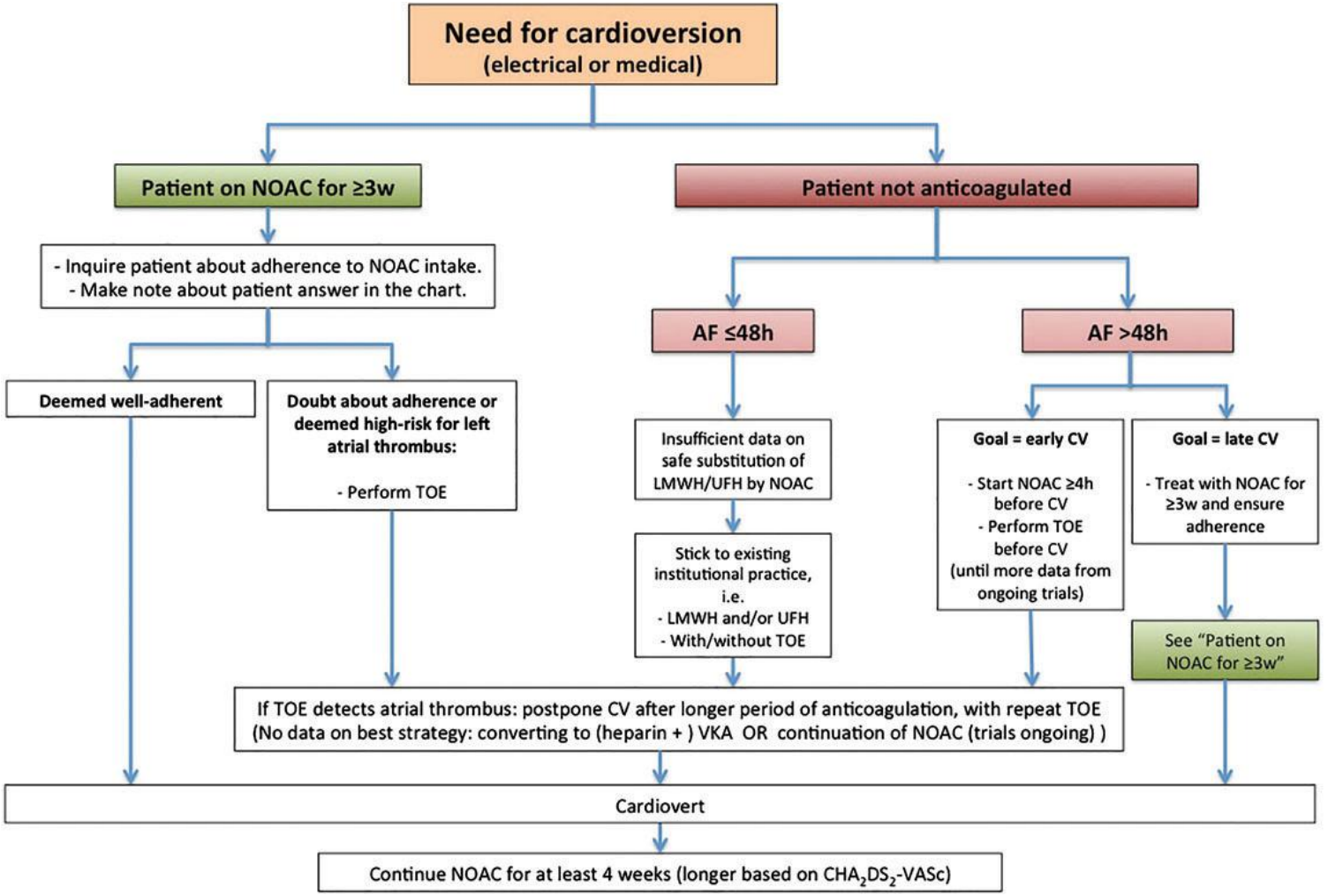
VI: Kardioverze a NOACs

Kardioverze FS



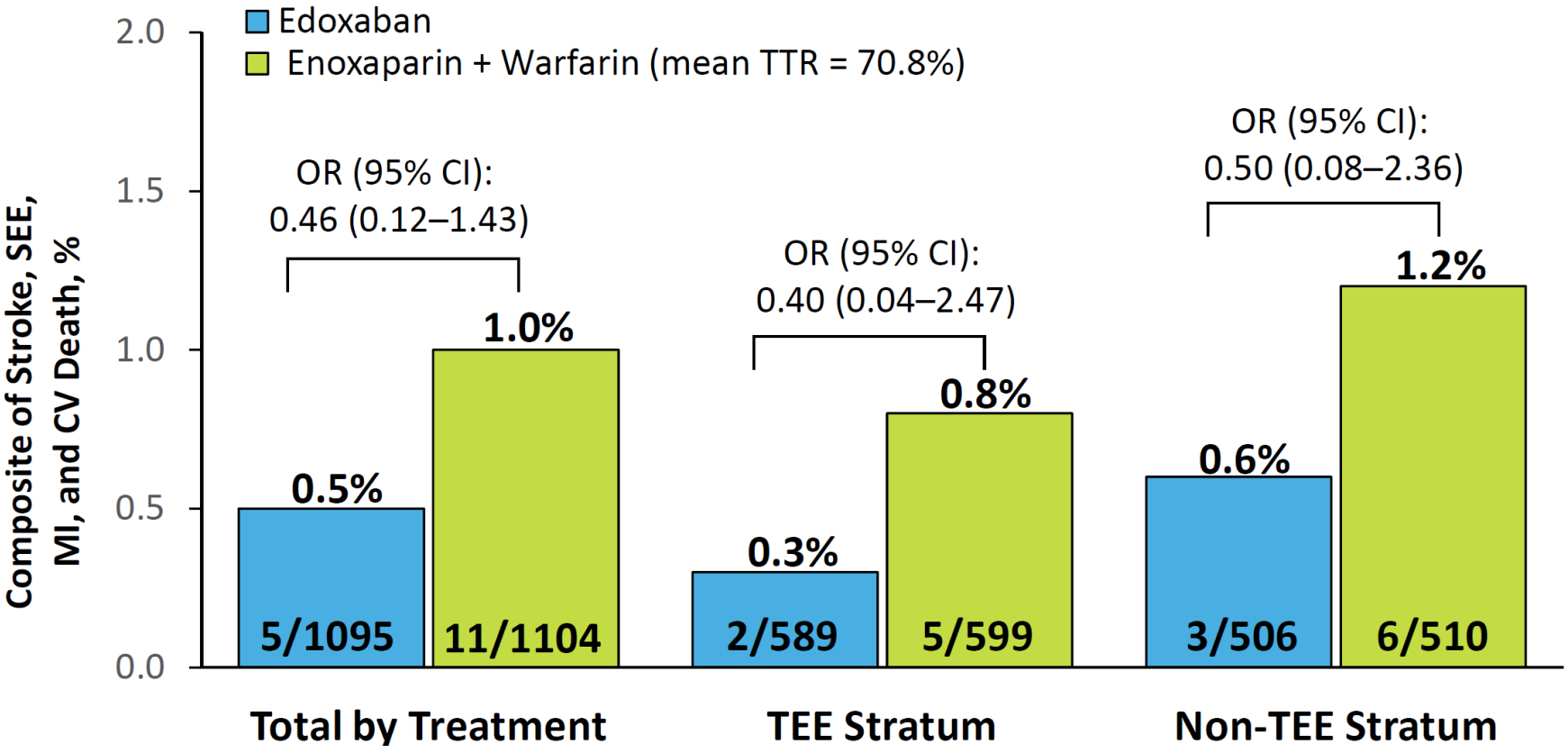
Heidbuchel H et al. Europace (2015) 17, 1467–1507
doi:10.1093/europace/euv309

X-VERT Study

	Total by treatment			Early		Delayed	
	Rivaroxaban	VKA	RR (95% CI)	Rivaroxaban	VKA	Rivaroxaban	VKA
Efficacy, *n* (%)[a]	*n* = 978	*n* = 492		*n* = 567	*n* = 277	*n* = 411	*n* = 215
Primary end-point	5 (0.51)	5 (1.02)	0.50 (0.15–1.73)	4 (0.71)	3 (1.08)	1 (0.24)	2 (0.93)
Stroke	2 (0.20)	2 (0.41)		2 (0.35)	1 (0.36)	0	1 (0.47)
Haemorrhagic stroke	2 (0.20)	0		2 (0.35)	0	0	0
Ischaemic stroke	0	2 (0.41)		0	1 (0.36)	0	1 (0.47)
TIA	0	0		0	0	0	0
SE	0	1 (0.20)		0	1 (0.36)	0	0
MI	1 (0.10)	1 (0.20)		1 (0.18)	0	0	1 (0.47)
Cardiovascular death	4 (0.41)	2 (0.41)		3 (0.53)	2 (0.72)	1 (0.24)	0
All-cause death	5 (0.51)	3 (0.61)		3 (0.53)	3 (1.08)	2 (0.49)	0
Safety, *n* (%)[b]	*n* = 988	*n* = 499		*n* = 575	*n* = 284	*n* = 413	*n* = 215
Major bleeding	6 (0.61)	4 (0.80)	0.76 (0.21–2.67)	3 (0.52)	3 (1.06)	3 (0.73)	1 (0.47)
Fatal	1 (0.10)	2 (0.40)		1 (0.17)	2 (0.70)	0	0
Critical site	2 (0.20)	3 (0.60)		2 (0.35)	2 (0.70)	0	1 (0.47)
ICH	2 (0.20)	1 (0.20)		2 (0.35)	0	0	1 (0.47)
Hb decrease ≥2 g/dL	4 (0.40)	1 (0.20)		1 (0.17)	1 (0.35)	3 (0.73)	0
Transfusion ≥2 units RBCs or whole blood	3 (0.30)	1 (0.20)		1 (0.17)	1 (0.35)	2 (0.48)	0

Cappato R et al. Eur Heart J. 2014 Dec 14;35(47):3346-55

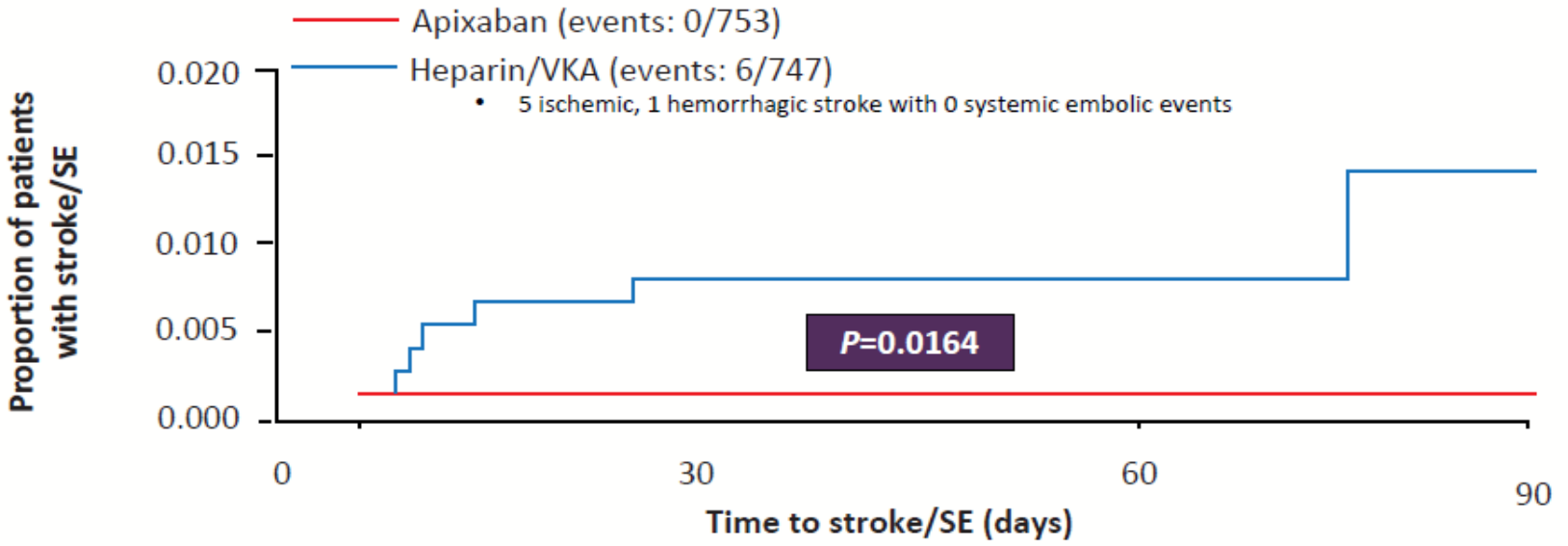
ENSURE-AF Study



Goette A:
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)31474-X/ppt

ENAMATE Study

Stroke/Systemic Embolic Outcomes



Number at risk

Apixaban	752	6145	199	55
Heparin/VKA	747	65	231	88

One patient's adjudicated stroke date was one day prior to randomization; thus at Day 0, only 1499 were at risk for stroke. No patients had SE.
ITT population. SE = systemic embolism

apixaban ***753 pts – 0 CMP, 3 závažná krvácení, 2 úmrtí***

heparin/warfarin ***747 pts – 6 CMP, 6 závažných krvácení , 1 úmrtí***

http://www.clinicaltrialresults.org/Slides/ESC2017/EMANATE_Ezekowitz.pdf

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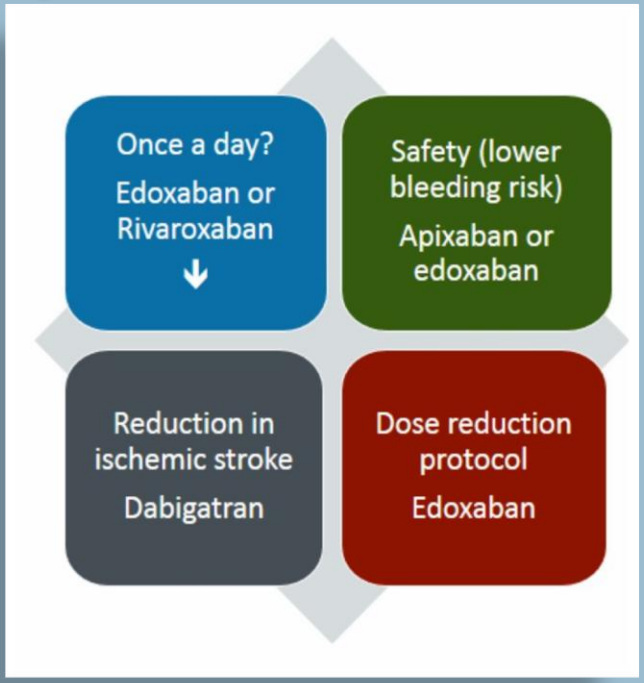
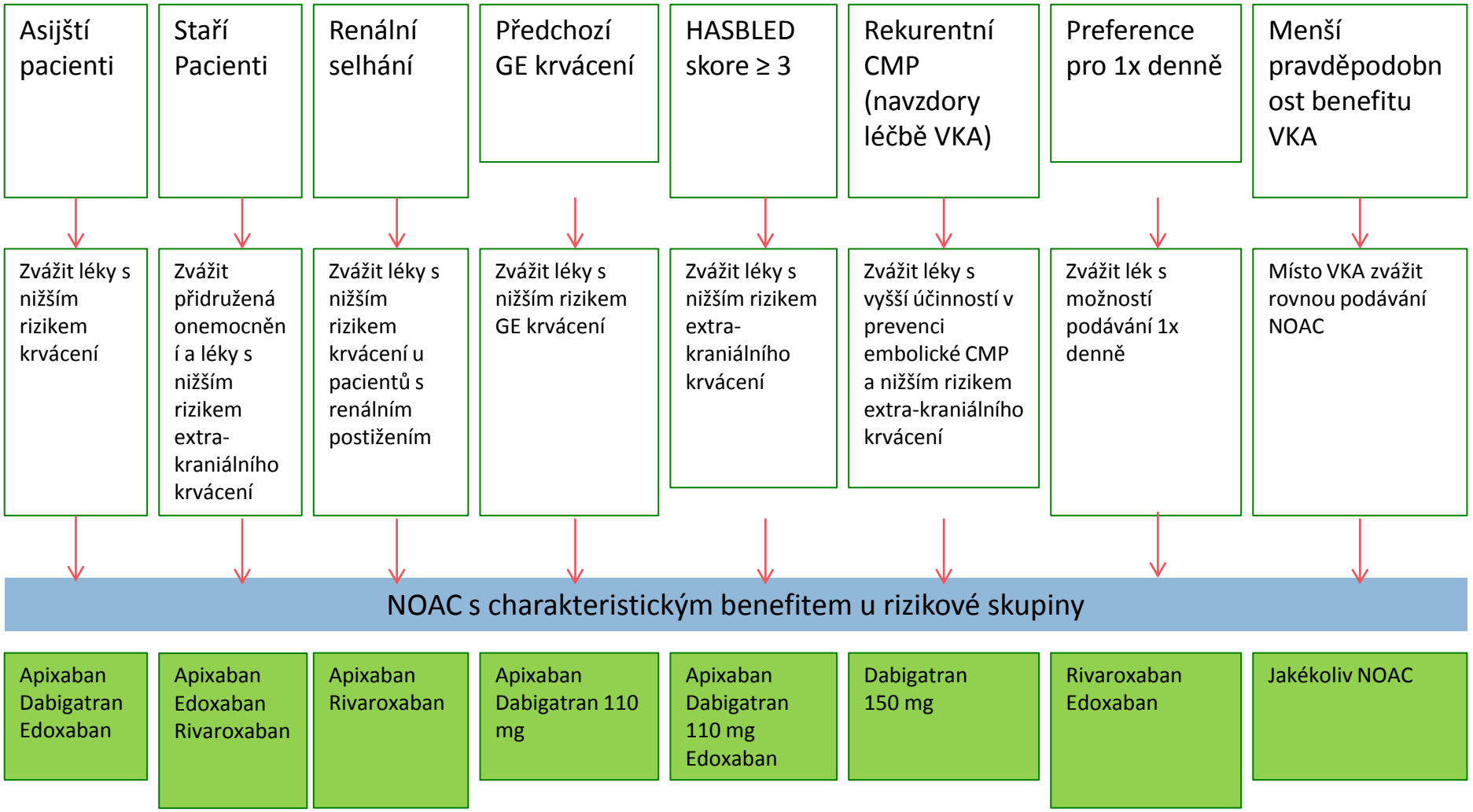
VII:Jaké NOAC pro jakého pacienta ???



Průkaz efektu NOACs u jednolivých indikací

NOAC	Fibrilace síní	Kardioverze	Snížení iCMP	AKS-PCI	HŽT/PE	ICHS/ICHDK	Ortopedie
Dabigatran	+	–	+	+	+	–	+
Rivaroxaban	+	+	–	+	+	+	+
Apixaban	+	+	–	–	+	–	+
Edoxaban	+	+	–	–	+	–	–
Betrixaban	studie	–	–	–	+	–	–

Individuální skupiny pacientů a charakteristiky



Shields AM, Lip GY. J Intern Med. 2015

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VIII: Upstream therapy, ablace FS u SS

Studie RACE 3

Risk factor driven upstream therapy is superior to conventional therapy for maintenance of sinus rhythm in patients with early persistent AF and heart failure

PE: Presence of sinus rhythm, defined as sinus rhythm during at least 6/7th of assessable time, at the 7-day Holter at 1-year

Risk factor driven upstream therapy

MRAs, ACE-Is and ARBs were dosed aiming to the highest tolerated dose

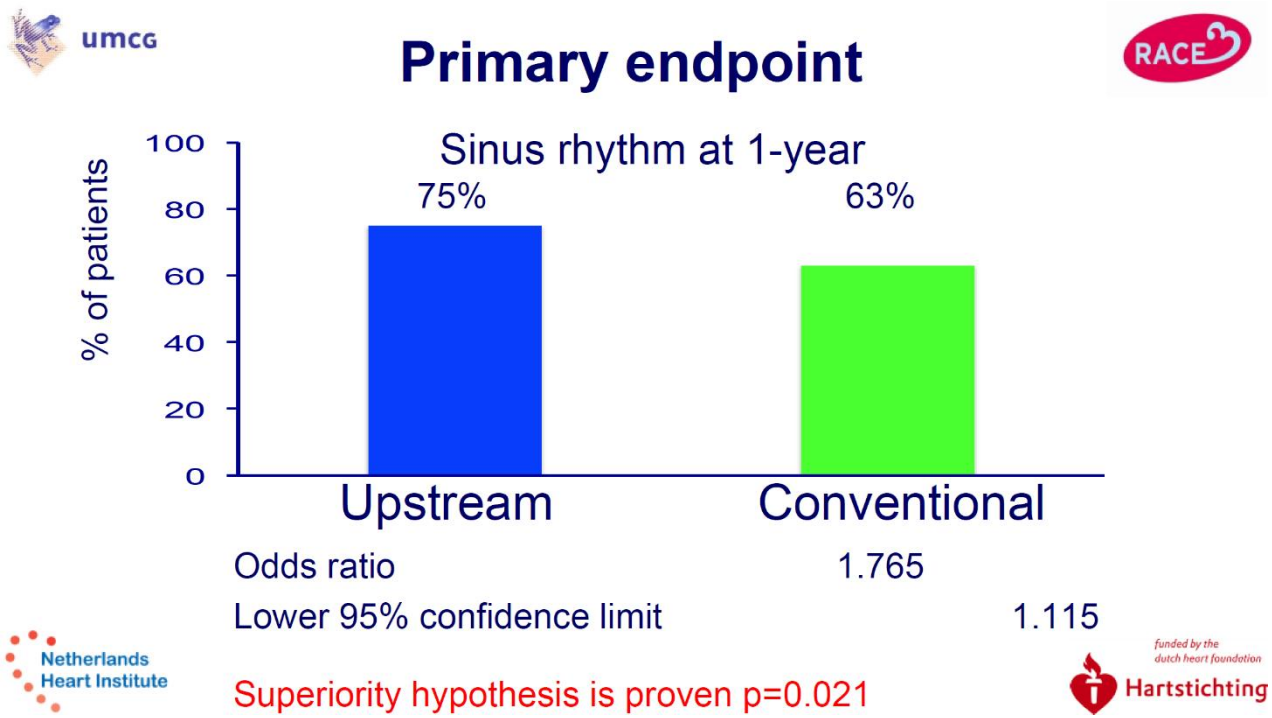
Blood pressure target was < 120/80 mmHg

Statins were prescribed at the recommended dosages

Physical activity and exercise maintenance

Dietary restrictions and drug adherence

Výsledky RACE 3



CASTLE-AF Study

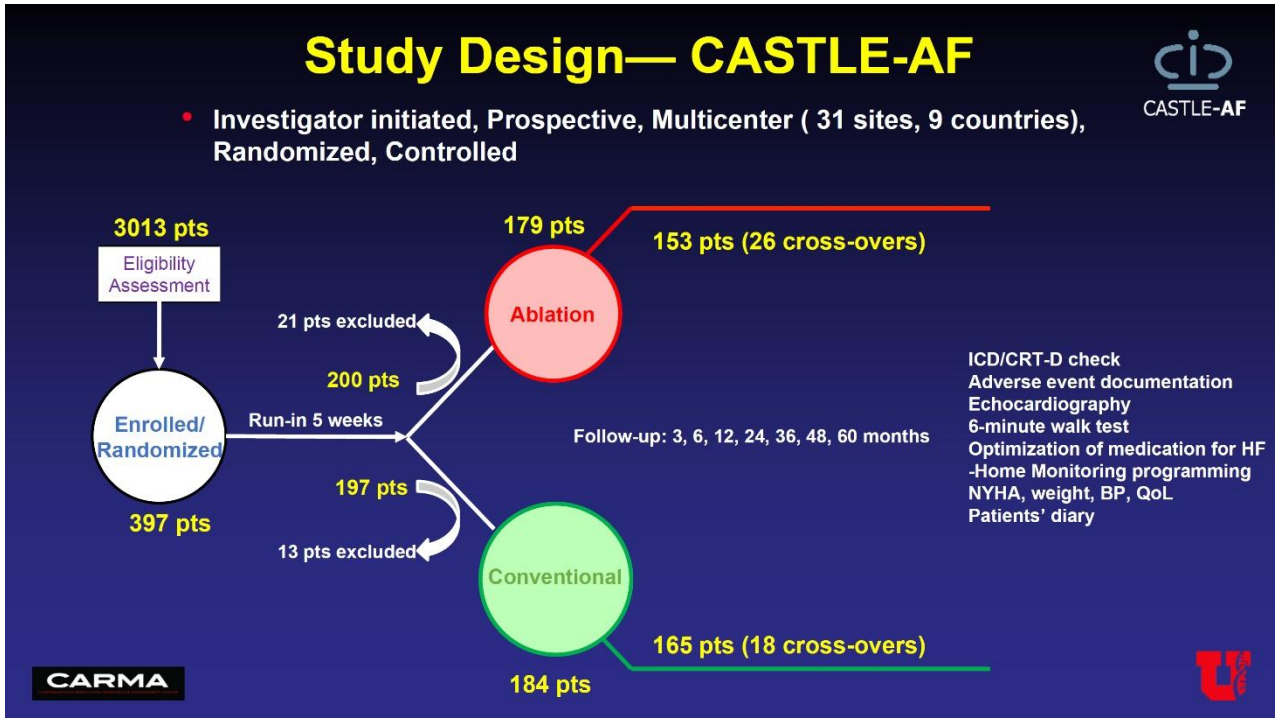
Study the effectiveness of *catheter ablation* of atrial fibrillation in patients with heart failure in *improving hard primary endpoints of mortality and heart failure progression* when compared to conventional standard treatment

Primary Endpoints:

All-cause mortality
Worsening heart failure Admissions

http://www.acc.org/latest-in-cardiology/articles/2017/08/16/13/24/sun11am-castle-af-catheter-ablation-conventional-therapy-patients-afib-lv-dysfunction-esc-2017

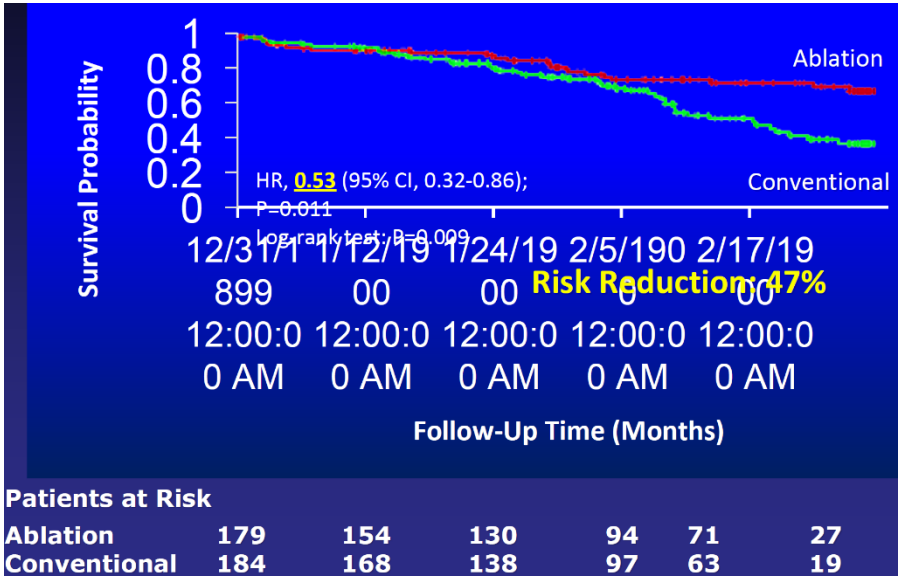
Study design



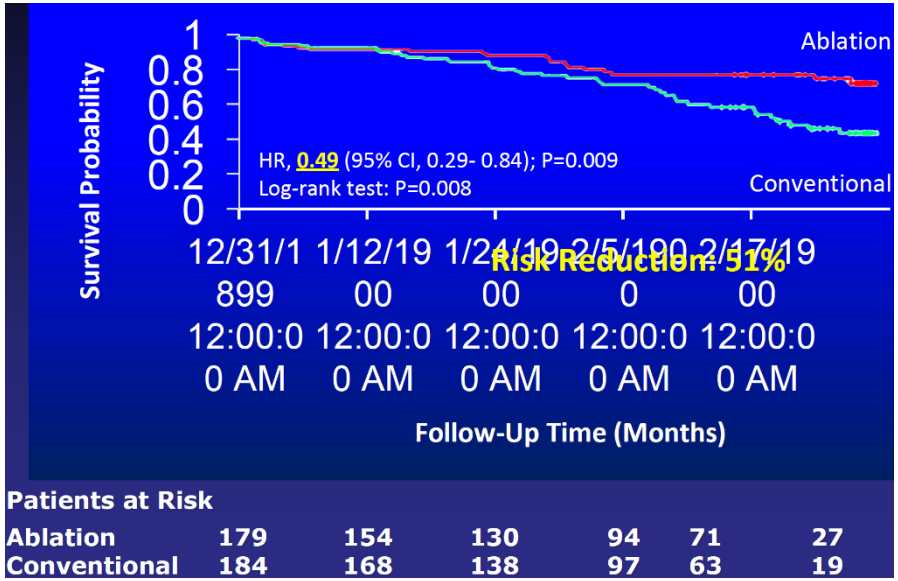
http://www.acc.org/latest-in-cardiology/articles/2017/08/16/13/24/sun11am-castle-af-catheter-ablation-conventional-therapy-patients-afib-lv-dysfunction-esc-2017

Výsledky

All-Cause Mortality



Cardiovascular Mortality



http://www.acc.org/latest-in-cardiology/articles/2017/08/16/13/24/sun11am-castle-af-catheter-ablation-conventional-therapy-patients-afib-lv-dysfunction-esc-2017

Take home mesage I

I: Volba konkrétního přímého perorálního antikoagulancia má být přísně individuální – posouzení řady kritérií:

1. Co je primárním medicínským cílem
2. Jak rizikový – fragilní je pacient
3. Jaké má komorbidity
4. Jaké má renální funkce
5. Posouzení otázky compliance a dlouhodobé perzistence k léčbě
6. Jaké je životní perspektiva pacienta
7. Otázka dávkování – nesnižovat neindikovaně dávky

Take home mesage II

II. U pacientů s FS podstupujícím PCI je evidentní nutnost změny od trojité terapie k duální terapii (NOAC + P2Y12 inhibitor) → snížení rizika krvácení, identická bezpečnost

III. Pravděpodobná je i indikace NOAC + ASA u pacientů se stabilní ICHS, PAD

IV. Kardioverze na NOAC je bezpečná a má být prováděna

V. Příchod dalších indikací lze jistě očekávat…

Srovnání podmínek úhrady NOACs v ČR x SR

Přípravek je hrazen v prevenci cévní mozkové příhody a systémové embolie u dospělých pacientů s nevalvulární fibrilací síní indikovaných k antikoagulační léčbě při kontraindikaci warfarinu, tj.:

	SR	ČR
PRIMÁRNÍ PREVENCE	a) chronická liečba warfarínom nie je dostatočne kontrolovaná v terapeutickom rozmedzí INR 2-3, t.j. dve merania zo šiestich nie sú v takto uvedenom terapeutickom rozmedzí, b) za prvé tri mesiace od začatia liečby warfarínom sa nedosiahne terapeutické rozmedzie INR 2-3 alebo c) liečba warfarínom je kontraindikovaná.	a) nemožnost pravidelných kontrol INR b) nežádoucí účinky při léčbě warfarinem c) nemožnost udržet INR v terapeutickém rozmezí 2,0 - 3,0; tzn. 2 ze 6 měření nejsou v uvedeném terapeutickém rozmezí d) rezistence na warfarin, tj. nutnost podávat denní dávku více než 10 mg
SEKUNDÁRNÍ PREVENCE	PRVNÍ LINIE	a) nemožnost pravidelných kontrol INR b) nežádoucí účinky při léčbě warfarinem c) nemožnost udržet INR v terapeutickém rozmezí 2,0 - 3,0; tzn. 2 ze 6 měření nejsou v uvedeném terapeutickém rozmezí d) rezistence na warfarin, tj. nutnost podávat denní dávku více než 10 mg

Zoznam kategorizovaných liekov 1.9.2017 – 30.9.2017, SR, Časť B: Indikačné obmedzenia (NOAK)

Cíle odborných společností

1. NOAC v první linii v sekundární prevenci TIA/iCMP

2. Odbourání stávajících limitací plátců zdravotní péče → respektování guidelines

3. NOAC po příslušné detailní edukaci v rukou PL

Děkuji za pozornost !